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Therapies for Children with Autism Spectrum Disorder—Behavioral Interventions Update

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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
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www.ahrq.gov

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Prepared by:
<redacted for peer review>

Investigators:
<redacted for peer review>

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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 can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. 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.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director, Agency for Healthcare Research and Quality

Stephanie Chang M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Joanna Siegel, RN, SM, SD
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Technical Expert Panel

[redacted for peer review]

Peer Reviewers

[to be added]

Therapies for Children with Autism Spectrum Disorder—Behavioral Interventions Update

Structured Abstract

Objective. We updated a prior systematic review of interventions for children (0-12 years) with autism spectrum disorder (ASD), focusing on recent studies of behavioral interventions.

Data sources. We searched the MEDLINE (PubMed), PsycInfo, and Educational Resources Information Clearinghouse (ERIC) databases as well as the reference lists of included studies and recent systematic reviews. We conducted the search in July 2013.

Methods. We included comparative (treatment and comparison groups) studies of behavioral interventions with at least 10 participants with ASD in the update, and made our conclusions based on the cumulative, comparative evidence across the original report and update.. Two investigators independently screened studies against predetermined inclusion criteria and independently rated the risk of bias of included studies.

Results. We included 51 unique studies comprising 37 randomized trials and 14 nonrandomized, comparative studies (16 good, 31 fair, and 4 poor quality) published since the prior review. The quality of studies improved compared with that reported in the earlier review. Young children receiving high intensity applied behavior analysis-based early intervention over extended time frames commonly displayed substantial improvement in cognitive functioning and language skills relative to community controlsThe magnitude of these effects varied across studies, potentially reflecting poorly understood modifying characteristics related to subgroups of children. Early intensive parent training programs modified parenting behaviors during interactions; however, data were more limited about their ability to improve developmental skills beyond language gains for some children. Social skills interventions varied in scope and intensity and showed some positive effects on social behaviors for older children in small studies . Evidence for play/interaction-based approaches suggested that joint attention interventions may be useful for young and preschool children with ASD when targeting joint attention skills; data on the effects of such interventions in other areas were limited. Studies examining the effects of CBT on anxiety report positive results in older children with average intelligence. Smaller, short-term studies of other interventions reported some improvements in areas such as sleep and communication, but data were too sparse to assess their overall effectiveness.

Conclusions. A growing evidence base suggests that behavioral interventions are associated with positive outcomes for children with ASD. Despite improvements in the quality of the included literature, a need remains for studies of interventions across settings and continued improvements in methodologic rigor. Substantial scientific advances are needed to move toward an enhanced understanding of which interventions are most effective for specific children with ASD.

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Executive Summary

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder marked by impaired social communication and social interaction accompanied by atypical patterns of behavior and interest. ASD is differentiated from other developmental disorders by significant impairments in social interaction and communication, along with restrictive, repetitive, and stereotypical behaviors and activities.[1] Social communication and social interaction features include deficits in social-emotional reciprocity (e.g., deficits in joint attention, atypical social approach and response, conversational challenges, reduced sharing of interest, emotions, and affect), deficits in nonverbal communication (e.g., atypical eye contact, reduced gesture use, limited use of facial expressions in social interactions, challenges understanding nonverbal communication), and deficits in forming and maintaining relationships (e.g., diminished peer interest, challenges joining in play, difficulties adjusting behavior to social context). ASD features of restricted, repetitive patterns of behavior, interests, or activities may include stereotyped motor mannerisms, use of objects, or speech (e.g., simple motor stereotypies, repetitive play, echolalia, and formal or idiosyncratic speech); insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior (e.g., distress at small changes, rigid patterns of thought and behavior, performance of everyday activities in ritualistic manner); intense preoccupation with specific interests (e.g., strong attachment to objects, circumscribed or perseverative topics of interest); and sensory sensitivities or interests (e.g., hyper- or hypo- reactivity to pain and sensory input, sensitivity to noise, visual fascination with objects or movement).[2-4] These symptoms cause impairment across many areas of functioning and are present early in life. However, impairments may not be fully evident until environmental demands exceed children's capacity. They also may be masked by learned compensatory strategies later in life. Many children with ASD may also have intellectual impairment or language impairment, and the disorder may be associated with known medical, genetic, or environmental factors.

Treatments for ASD include behavioral, educational, medical, allied health, and complementary approaches. Individual goals for treatment vary for different children and may include combinations of therapies. For many individuals, core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and over time[5-8]; however, deficits typically remain throughout the lifespan. Chronic management—often using multiple treatment approaches—may be required to maximize ultimate functional independence and quality of life.

Scope and Key Questions

This systematic review updates the behavioral intervention portion of our comprehensive review of therapies for children with ASD published in 2011.[9] At that time, the strength of the evidence was considered low for the effectiveness of early intensive behavioral and developmental interventions. Positive outcomes from an early and intensive behavioral and developmental intervention were noted in cognitive performance, language skills, and adaptive behavior when the intervention was delivered over substantial intervals of time (i.e., 1–2 years). Variability in response to such approaches was tremendous, with subgroups of children who demonstrated a more moderated response. The ability to describe and predict these subgroups is limited.

Some other behavioral and educational interventions that varied widely in terms of scope, target, and intensity had demonstrated effects, but the lack of consistent data limited understanding of whether these interventions are linked to specific clinically meaningful changes in functioning. Information was similarly lacking on modifiers of effectiveness, generalization of effects outside the treatment context, components of multicomponent therapies that drive effectiveness, and predictors of treatment success.

Since the publication of the initial review in 2011, a sizable body of research has been published, particularly addressing behavioral interventions. Additional studies of behavioral interventions have the greatest potential to alter the low and insufficient strength of evidence reported in the original review and potentially affect treatment recommendations due to the number of new studies available. For this reason, the current review update focuses on studies of behavioral interventions.

Key Questions

We focused this review on behavioral treatments for children ages 2-12 with ASD and children younger than age 2 at risk of a diagnosis of ASD. We have synthesized evidence in the published literature to address these key questions (KQ):

KQ1: Among children ages 2-12 with ASD, what are the short and long-term effects of available behavioral 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 behavioral 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)?

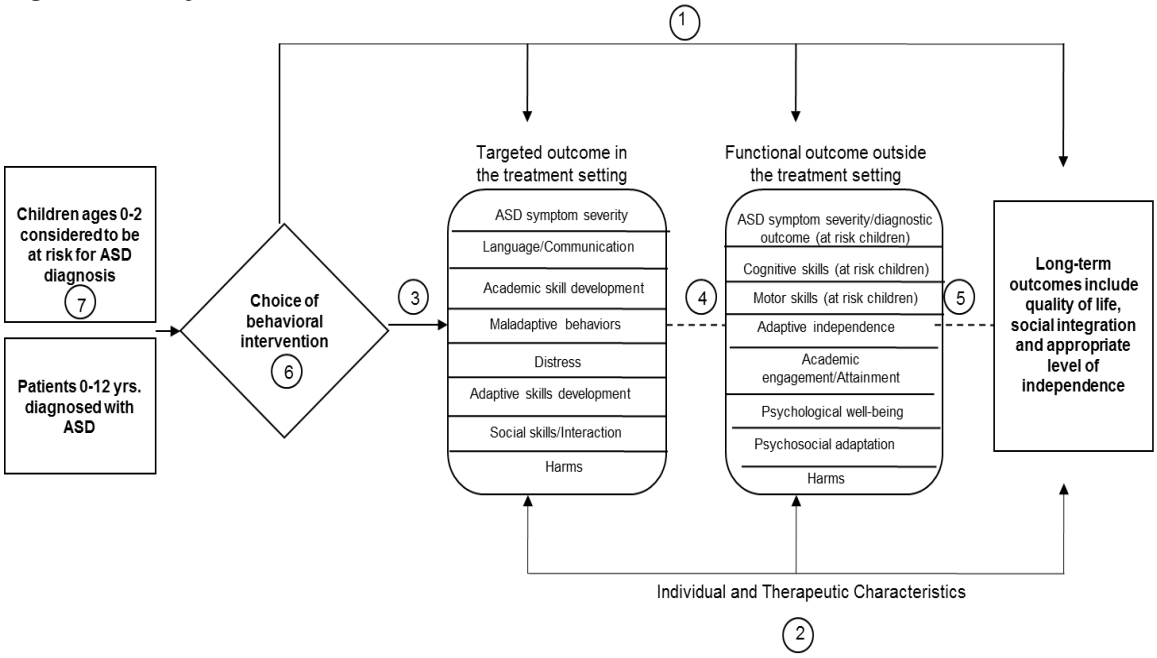
KQ6: What evidence supports specific components of behavioral treatment as driving outcomes, either within a single treatment or across treatments?

KQ7: What evidence supports the use of a specific behavioral 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

Figure A illustrates the analytic framework for the current update. The figure summarizes the process by which families of children with ASD make and modify treatment choices.

Figure A. Analytic framework for behavioral interventions for children with ASD



ASD=autism spectrum disorder; KQ=key question.

Methods

Literature Search Strategy

A librarian employed search strategies provided in Appendix A of the full report to retrieve research on interventions for children with ASD. We searched MEDLINE® via the PubMed interface, PsycINFO® (psychology and psychiatry literature), and the Educational Resources Information Clearinghouse using a combination of subject heading terms appropriate for each database and key words relevant to ASD (e.g., autism, Asperger). We limited searches to the English language and literature published since the development of the 2011 review. Our last search was conducted in July 2013. We also manually searched the reference lists of included studies and of recent narrative and systematic reviews and meta-analyses addressing ASD.

Inclusion and Exclusion Criteria

We developed criteria for inclusion and exclusion based on the patient populations, interventions, outcome measures, and types of evidence specified in the key questions and in consultation with a Technical Expert Panel. Table A summarizes criteria.

Table A. Inclusion criteria

Category	Criteria
Study population	Children ages 0-12 with ASD or 0-2 considered to be at risk for ASD based on sibling status or early developmental/behavioral vulnerabilities highly suspicious of ASD
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs RCTs, prospective and retrospective cohort studies, and nonrandomized controlled trials 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 and ≥ 10 participants with ASD Studies must address one or more of the following for ASD: -Behavioral treatment modality -Predictors of treatment outcomes -Generalization of treatment outcomes to other contexts -Drivers of treatment outcomes Relevant outcomes must be able to be abstracted from data in the papers Data must be presented in the aggregate (vs. individual participant data)

ASD-autism spectrum disorder; RCT-randomized controlled trial

Study Selection

Two reviewers independently assessed each abstract identified for potential inclusion using an abstract review form using questions stemming from our selection criteria. If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it for full text assessment. Two reviewers independently assessed the full text of each included study using a similar standardized form. Disagreements between reviewers were resolved by a third-party adjudicator. The group of abstract and full text reviewers included expert clinicians and researchers and health services researchers; abstract and full text review forms are in Appendix B of the full report.

Data Extraction

We extracted data from included studies into evidence tables that report study design, descriptions of the study populations (for applicability), description of the intervention, and baseline and outcome data on constructs of interest. Data were initially extracted by one team member and reviewed for accuracy by a second. The final evidence tables are presented in their entirety in Appendix C of the full report. For those studies reported in the 2011 review and with follow-up data reported here, the evidence table for the original studies can be found in the 2001 report.[9]

Risk of Bias Assessment

We used the components approach to assessing the quality of individual studies developed for the 2011 review and following methods outlined in the Agency for Healthcare Research and Quality Effective Health Care program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[10] We assessed the quality of studies in the domains including study design, participant ascertainment, diagnostic approach, and outcomes measurement using specific questions to evaluate a study's conduct. We rated each domain individually and

combined them for an overall quality level as described in the full report. Three levels were possible: good, fair, and poor

Data Synthesis

We summarized all data qualitatively using evidence tables. We focused on outcomes related to core ASD symptoms (impairments in communication and social interaction and restricted/repetitive behaviors and interests) and key symptoms in studies of interventions targeting conditions commonly associated with ASD (e.g., anxiety). For the update, we describe new comparative studies published since the original report, and we make our conclusions and assess the strength of evidence on the cumulative, comparative evidence across the original report and update.

Strength of the Body of Evidence

Two senior investigators graded the entire body of evidence (i.e., studies from 2011 review and studies identified for the current review) based on the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[10] The team reviewed the final designation. The assessment of the literature is done by considering both the observed effectiveness of interventions and the confidence that we have in the stability of those effects in the face of future research. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence, and it can be regarded as insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, both in terms of quantity and quality, as well as the degree to which the entire body of current research provides a consistent and precise estimate of effect. Once we had established the maximum strength of evidence possible based upon criteria for each domain (study limitations, consistency in direction of the effect, directness in measuring intended outcomes, precision of effect, and reporting bias), we assessed the number of studies and range of study designs for a given intervention-outcome pair and downgraded the rating when the cumulative evidence was not sufficient to justify the higher rating. The possible grades were:

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

Applicability

We assessed applicability by identifying potential population, intervention, comparator, outcomes, and setting (PICOS) factors likely to affect the generalizability of results. For this particular review, the most likely factors that could affect applicability are the patient population (e.g. whether or not results are available to assess the utility of given interventions in target populations) and the intervention (e.g., the difficulty of applying the intervention in a non-research setting given available resources). We noted where data were available for specific populations and made relative assessments of applicability for intervention components in the context of resource considerations.

Results

Article Selection

We identified 2193 newly published citations and abstracts (disposition of studies figure in the full report). We excluded 1698 studies at abstract review and assessed the full text of 495 studies. Among these, 62 publications, comprising 51 unique studies, met our criteria. Seven of these studies report followup data to papers included in the 2011 review of therapies for children with ASD. The 51 new studies described in this update to add to the conclusions of the original report comprise 37 randomized controlled trials (RCTs) and 14 nonrandomized trials or cohort studies. The full report includes detailed references. Appendix E of the full report includes a list of all studies excluded at the abstract and full-text review stages.

KQ1. Effects of Behavioral Interventions on Core and Commonly Associated Symptoms in Children With ASD

Early Intensive Behavioral and Developmental Interventions

We located 31 papers comprising 21 unique studies addressing early intensive behavioral and developmental interventions. Individual studies using intensive University of California. Los Angeles (UCLA)/Lovaas-based interventions, the Early Start Denver Model (ESDM), the Learning Experiences and Alternate Program for Preschoolers and their Parents (LEAP) program, and eclectic variants reported improvements in outcomes for young children. Improvements were most often seen in cognitive abilities and language acquisition with less robust and consistent improvements seen in adaptive skills, core ASD symptom severity, and social functioning.

Young children receiving high intensity applied behavior analysis (ABA)-based interventions over extended time frames (i.e., 8 months--2 years) commonly displayed substantial improvement in cognitive functioning and language skills relative to community controls (Table B). However, the magnitude of these effects varies across studies and this variation may reflect subgroups showing different responses to particular interventions. Intervention response is likely moderated by both treatment and child factors, but exactly how these moderators function is not entirely clear. Despite multiple studies of early intensive treatments, intervention approaches still vary substantially, which makes it difficult to tease apart what these unique treatment and child factors may be. Further, the long-term impact of these early skill improvements is not yet clear, and many studies did not follow children beyond late preschool or early school years.

Studies of high intensity early intervention services also demonstrated improvements in children's early adaptive behavior skills, but these improvements are more variable than those found for early cognitive and language skills. Treatment effects are not consistently maintained across studies. Many studies measure different adaptive behavior domains (which creates within scale variability) and some evidence suggests that adaptive behavior changes may be contingent upon baseline child characteristics, such as cognitive/language and autism severity.

Evidence for the impact of early intensive intervention on core ASD symptoms is limited and mixed. Children's symptom severity often decreased during treatment, but these improvements did not often differ from those of children in control groups. In fact, almost equal numbers of studies report treatment impact versus null treatment effects.

Since our previous review, there have been substantially more studies of well-controlled, low intensity interventions that provide parent training in bolstering social communication skills. However, although parent training programs certainly modified parenting behaviors during interactions, data are more limited about their ability to improve broad developmental skills (such as cognition, adaptive behavior, and ASD symptom severity) beyond language gains for some children. Children receiving low-intensity interventions have not demonstrated the same substantial gains as seen in the early intensive intervention paradigms regarding cognitive and adaptive skills.

Social Skills Studies

We located 10 studies addressing interventions targeting social skills. The overall quality of studies improved in comparison to the previous review with two good quality and eight fair quality studies. Social skills interventions varied widely in terms of scope and intensity. A few studies replicated interventions using the manualized Skillstreaming model; other studies incorporated peer-mediated and/or group-based approaches, and still others described interventions that focused on emotion identification and theory of mind training. The studies also varied in intensity, with most interventions consisting of 1-2 hour sessions/week lasting for approximately 4-5 weeks. However, some of the group-based approaches lasted for 15-16 weeks.

Most studies reported short term gains in either parent-rated social skills or directly tested emotion recognition. However, our confidence (strength of evidence) in that effect is low (Table B). While we now have higher quality investigations of social skills interventions demonstrating positive effects, our ability to determine the effectiveness of these interventions continues to be limited by the diversity of the intervention protocols and measurement tools (i.e., no consistent outcome measures used across studies). Maintenance and generalization of these skills beyond the intervention setting is also inconsistent, with parent- and clinician-raters noting variability in performance across settings.

Play- /Interaction-Focused Studies

Since our previous review, more studies of well-controlled joint attention interventions across a range of intervention settings (e.g., clinician, parent, teacher delivered) have been published. This growing evidence base suggests that joint attention interventions may be useful for young and preschool children with ASD, particularly when targeting joint attention skills themselves as well as related social communication and language skills (Table B). Although joint attention intervention studies certainly demonstrated changes within this theoretically important domain, data are more limited about their ability to improve broad developmental skills (such as cognition, adaptive behavior, and ASD symptom severity) beyond communication and language gains over time.

Specific and focal training regarding imitation skills utilizing naturalistic approaches to promote imitation (i.e., Reciprocal Imitation Training) was associated with some positive results in improving not only imitation skills, but potentially other social communication skills such as joint attention as well. Additionally, parent training in a variety of play-based interventions also was associated with positive results for encouraging early social communication skills (e.g., joint attention, engagement, play interactions), play skills, and early language skills.

Interventions Targeting Conditions Commonly Associated With ASD

Five of six RCTs identified in the literature measured anxiety symptoms as a primary outcome. Four of these studies reported significantly greater improvements in anxiety symptoms in the intervention group compared with controls. Two of these studies found positive effects of cognitive behavioral therapy (CBT) on the core autism symptom of socialization. The one RCT that did not find a significant benefit of CBT compared it to social recreational therapy rather than treatment as usual or a waitlisted control group.

The studies examining the effects of CBT on anxiety had largely consistent methodologies and primarily conducted weekly 60-90 minute treatment sessions over a period of 4 months. All studies provided followup data reflecting treatment effects that lasted beyond the period of direct intervention. Two common factors limit the applicability of the results, however. Due to the nature of CBT, which is often language-intensive and requires a certain level of reasoning skills to make abstract connections between concepts, most studies included only children with IQs much greater than 70. These studies report positive results regarding the use of CBT to treat anxiety in children with ASD (Table B). They also suggest that CBT could potentially be related to improvements in socialization and communication, although these results were less robust and it is unclear if these improvements were beyond improvements related to the impact of ameliorated anxiety itself.

Additional data in the current review relate to parent training to address challenging behavior. Specifically, one fair quality study combined a parent training approach with risperidone. This combination significantly reduced irritability, stereotypic behaviors, and hyperactivity, and improved socialization and communication skills. However, these effects were not maintained at one-year post-treatment.

Other Behavioral Studies

Two studies examined neurofeedback and found some improvements on parent-rated measures of communication and tests of executive function. Two studies reported on sleep-focused interventions, with little positive effect of a sleep education pamphlet for parents in one and improvements in sleep quality in treatment arms (melatonin alone, melatonin+CBT) in another.

KQ2. Modifiers of Treatment Effects

Among early intensive ABA-based interventions potential modifiers or moderators, younger age at intake was generally associated with better outcomes for children; however, this finding was not present in many studies. Higher cognitive skills and higher adaptive behavior scores at baseline were also often associated with better outcomes across behavioral interventions, but the associations were not consistent. In general, children with lower symptom severity or less severe diagnoses improved more than participants with greater impairments. However, many studies (e.g., social skills, CBT) often restricted the range of participants' impairment at baseline, limiting understanding of intervention impact on broader populations. Studies assessing parental responsiveness to children's communication typically reported better outcomes in children whose parents were more aligned with the child's communication versus those who attempted to re-direct or were less synchronized with it. Regarding intervention-related factors, duration of treatment had an inconsistent effect, with some studies reporting improved outcomes with

greater intervention time and others reporting no association. Studies have often most often not been adequately designed or controlled in order to help identify true moderators of treatment.

KQ3. Treatment Phase Changes That Predict Outcomes

Information about early response to treatment (or lack thereof) could guide treatment selection, implementation, and modification. The reviewed literature offers little information about what specific early changes from baseline measurements of child characteristics might predict long-term outcome and response. Some evidence suggests that the best predictor of long-term outcome is not baseline characteristics at all, but rather the magnitude of change seen over the course of treatment (e.g., cognitive shifts in first years of early intensive treatments).

KQ4. Treatment Effects That Predict Long-Term Outcomes

Few studies assess end-of-treatment effects that may predict outcomes. Several early intensive behavioral and developmental intervention paradigms change measures over the course of very lengthy treatments, but such outcomes usually have not been assessed beyond treatment windows. One family of studies attempted to follow young children receiving early joint attention intervention until they were school aged, but this study failed to include adequate followup of control conditions. It also involved children were receiving many hours of uncontrolled interventions during the course of study.

KQ5. Generalization of Treatment Effects

The majority of the social skills and behavioral intervention studies targeting associated conditions attempted to index outcomes based on parent, self, teacher, and peer report of targeted symptoms (e.g., anxiety, externalizing behaviors, social skills, peer relations) at home, at school, and in the community. While such ratings outside of the clinical setting may be suggestive of generalization in that they improve outcomes in the daily context/life of the child, in most cases, these outcomes are parent reported and not confirmed with direct observation. Behavioral intervention studies rarely measured outcomes beyond the intervention period, and therefore we cannot assume that effects are maintained over time.

KQ6. Treatment Components That Drive Outcomes

We did not identify any studies meeting our inclusion criteria that addressed this question.

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

In the studies addressing interventions for younger children, children who received behavioral interventions seemed to improve regardless of intervention type. None of the fair or good quality studies compared treatment groups to a no treatment control group. Potential modifiers of treatment efficacy include baseline levels of object interest. Most outcome measures of adaptive functioning were based upon parent report, and the effect of parental perception of treatment efficacy on perception (and report) of child functioning was generally not explored.

Discussion

Key Findings and Strength of Evidence

Since our previous review in 2011, there has been a significant increase in the quantity and quality of studies investigating behavioral interventions. These new studies add to the prior report and strengthen our ability to make conclusions about the effectiveness of behavioral interventions. Of the 45 comparative studies of behavioral interventions (29 RCTs) in the 2011 review, we considered only two as good quality. Among the new studies described in this current review, 16 studies are good quality, and 37 of the 51 included studies are RCTs.

Considerable and consistent evidence from the original report and this update suggests that early behavioral and developmental intervention based on the principles of ABA delivered in intensive (≥15 hours per week) and comprehensive (i.e., addressing numerous areas of functioning) form significantly and positively affects the development of children with ASD (Table B). Across approaches, children receiving early intensive behavioral and developmental interventions demonstrate improvements in cognitive, language, adaptive, and ASD impairments compared with children receiving low-intensity interventions and eclectic non-ABA based intervention approaches.

Since our previous review, there have also been substantially more studies of well-controlled low intensity interventions aimed at parent training for comprehensive impact on social communication skills. This growing evidence base suggests that such interventions may be useful for very young children when targeting social communication and language use. However, although parent training programs certainly modified parenting behaviors during interactions, data are more limited about their ability to improve broad developmental skills (such as cognition, adaptive behavior, and ASD symptom severity) beyond short-term language gains for some children.

A growing number of studies of improved quality have demonstrated benefit of social skills interventions on at least one outcome measure, but a lack of consistency in the interventions studied and outcome measures utilized makes it difficult to understand the consistency or precision of impact across intervention modes.

An increasing evidence base also suggests that children receiving targeted play-based interventions (e.g., joint attention, imitation, play-based interventions) demonstrate improvements in early social communication skills. Children receiving targeted joint attention packages in combination with other interventions show substantial improvements in joint attention and language skills over time. There is also evidence across a variety of play-based interventions that young children may display short-term improvements in early play, imitation, joint attention, and interaction skills. However, there is not substantial evidence that these short-term improvements are linked to broader indices of change over time.

CBT for associated conditions such as anxiety had the largest number of high quality studies in the current review. A strong evidence base now suggests that school-aged children with average to above average intelligence and comorbid anxiety symptoms receiving manualized CBT therapy show substantial improvements in anxiety compared with wait-list controls. Table B summarizes the strength of the evidence for each category of intervention.

Table B. Strength of the evidence

Intervention	Outcome	Strength of Evidence	Study Design (N participants)/ Risk of Bias	Domain Ratings, Issues, and Findings
Early intensive behavioral and developmental intervention: ABA-based	**IQ/ Cognitive**	Moderate	RCT: 2 good, 1 fair (360) nRCT: 4 fair (130) Prospective cohort: 6 fair, 2 poor (521) Retrospective cohort: 1 fair, 2 poor (182)	Study limitations: Medium Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Approaches across studies vary substantially; difficult to determine the effects of these unique studies on impacting specific groups of children Findings: Young children receiving high intensity interventions display improvements in aspects of cognitive functioning. Most studies found that children in treatment and comparison groups both improved on cognitive skills, with children in EIBI interventions (target intervention) improving more than children receiving other types of services (eclectic comparators). Not all improvements maintained at long-term followup Therefore, SOE was moderate for a positive effect relative to eclectic controls.
	Adaptive behavior	Low	RCT: 1 good, 1 fair (76) nRCT: 4 fair (130) Prospective cohort: 7 fair, 2 poor (616) Retrospective cohort: 1 fair, 2 poor (182)	Study limitations: Medium Consistency: Inconsistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Other concerns: Always measured by parent report (Vineland) rather than objective observation Findings: Most studies found that children in both treatment and control groups improved on adaptive skills. However, children in EIBI interventions improved more than children receiving other types of services. Not all group differences maintained over long-term followup Therefore, SOE was low for a positive effect relative to eclectic controls.
	Symptom severity	Low	RCT: 1 good, 1 fair (332) nRCT: 1 fair (34) Prospective cohort: 4 fair, 2 poor (470) Retrospective cohort: 1 fair (142)	Study limitations: Medium Consistency: Inconsistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Other concerns: Most control groups were also receiving treatments and also showed improvement, making it difficult to tease apart the effect of intervention Findings: Mixed impact on symptom severity, with approximately equal numbers of studies finding and not finding treatment effects. Therefore, SOE was low for an unclear effect relative to eclectic controls

Table B. Strength of the evidence, continued

Intervention	Outcome	Strength of Evidence	Study Design (N participants)/ Risk of Bias	Domain Ratings, Issues, and Findings
Early intensive behavioral and developmental intervention: ABA-based	**Language/ Commun-ication**	Moderate	RCT: 1 good, 2 fair (360) nRCT: 3 fair (103) Prospective cohort: 6 fair, 2 poor (616)	Study limitations: Medium Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Some studies measured language using direct testing, whereas others only used the Vineland Communication domain Findings: Most studies found a positive effect of treatment on language/communication skills, although the specific domain of improvement (e.g., receptive vs. expressive language) varied across study. Some initial between-group differences disappeared at long-term follow-up There is moderate SOE of a positive effect on language overall.
	Social skills/social behavior	Low	RCT: 1 good, 1 fair (332) nRCT: 1 fair (34) Prospective cohort: 4 fair, 1 poor (406) Retrospective cohort: 1 fair (142)	Study limitations: Medium Consistency: Inconsistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Other concerns: Social skills were assessed almost exclusively using parent-reported standard scores on the Vineland Findings: Many studies found that treatment groups improved more than controls on measures of social skills, although a significant minority did not find any treatment effect Strength of evidence is low at this time because although positive effects were observed they were not consistent.
Early intensive behavioral and developmental intervention: parent training	**IQ/Cognitive**	Low	RCT: 1 good, 3 fair (232) Prospective cohort: 1 good, 1 fair (110)	Study limitations: Medium Consistency: Inconsistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Other concerns: None Findings: Few early intervention-parent training studies examined cognitive skills Of those that did, two found that treatment groups improved more than controls and two found no treatment effects

Table B. Strength of the evidence, continued

Intervention	Outcome	Strength of Evidence	Study Design (N participants)/ Risk of Bias	Domain Ratings, Issues, and Findings
Early intensive behavioral and developmental intervention: ABA-based	**Symptom severity**	Low	RCT: 3 good, 3 fair (361) Prospective cohort: 1 good, 1 fair, 1 poor, (171)	Study limitations: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Other concerns: Measure of symptom severity varied across studies and was inconsistently defined Findings: Many studies found that treatment groups had improved autism symptoms relative to controls
	Language / commun-ication	Moderate	RCT: 3 good, 5 fair, 1 poor (574) nRCT: 1 poor (22) Prospective cohort: 2 good, 1 poor (144)	Study limitations: Low Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Mix of outcome measures—both parent reported (VABS) and more standardized measures like Reynell or Mullen Findings: Some studies found differential impacts of treatment type on language comprehension vs. expression, although results were mixed, with many studies not finding treatment effects
Social Skills	**Social skills/ social behavior**	Low	RCT: 2 good, 10 fair, 5 poor (696) nRCT: 1 fair (21) Retrospective cohort: 1 poor (117)	Study limitations: Medium Consistency: Inconsistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Interventions varied widely in terms of scope and intensity Findings: School-aged children diagnosed without concomitant cognitive and language deficits demonstrated short-term gains in social skills and emotion recognition. Maintenance and generalization of these skills beyond the treatment context had variable results

Table B. Strength of the evidence, continued

Intervention	Outcome	Strength of Evidence	Study Design (N participants)/ Risk of Bias	Domain Ratings, Issues, and Findings
Interventions addressing commonly associated conditions: CBT	**Anxiety**	High (for older children with at least average IQs)	RCT: 6 good, 2 poor (401) nRCT: 1 fair (31)	Study limitations: Low Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Studies included older children, typically with IQ>70 Findings: Improvement in anxiety symptoms greater for CBT vs. control group in 5/6 studies; study that did not show improvement compared CBT to an active treatment instead of a waitlisted control. Improvements maintained at followup
	Symptom severity	Low	RCT: 2 good (81)	Study limitations: Low Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Findings: Improvement in severity of symptoms had large effect in both studies. Improvement was maintained at followup.
Interventions addressing commonly associated conditions: parent training	**Challenging behavior**	Low	RCT: 1 fair, 1 poor (146) Prospective cohort: 1 poor (106)	Study limitations: Medium Consistency: Consistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Other concerns: Measures of challenging behavior in the good-quality study were all based on parent report. Findings: Improvement in challenging behavior was demonstrated in both studies examining effects of parent training. In the study that performed one year followup, differences in improvement were lost. However the sample size was significantly smaller.
Play/ interaction based interventions	**Joint attention**	Moderate	RCT: 3 good, 3 fair (213)	Study limitations: Low Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Children in several studies were also receiving other early intervention; disentangling results is difficult Findings: Selected joint attention skills consistently increased in treatment arms, but duration of effects is unclear

Table B. Strength of the evidence, continued

Intervention	Outcome	Strength of Evidence	Study Design (N participants)/ Risk of Bias	Domain Ratings, Issues, and Findings
Play/ interaction based interventions	**Play skills**	Low	RCT: 3 good, 1 fair, 3 poor (196) Prospective cohort: 1 poor (12)	Study limitations: Medium Consistency: Consistent Directness: Direct Precision: Precise Reporting bias: Undetected Other concerns: Children in several studies were also receiving other early intervention; disentangling results is difficult Findings: Play skills increased in treatment arms but duration of effects is unclear. Imitation skills improved in treatment arms in 4 small, short-term studies
	Language/ Commun-ication	Low	RCT: 3 fair (142)	Study limitations: Medium Consistency: Consistent Directness: Direct Precision: Imprecise Reporting bias: Undetected Children in several studies were also receiving other early intervention; disentangling results is difficult Findings: Expressive but not receptive language skills generally increased in the treatment arms in 2 studies; prompted but not spontaneous communication improved in 1 study
	Social skills	Low	RCT: 1 good, 3 fair (173)	Study limitations: Medium Consistency: Consistent Directness: Indirect Precision: Precise Reporting bias: Undetected Children in several studies were also receiving other early intervention; disentangling results is difficult Findings: Joint engagement or positive affect improved in treatment arms in 3 studies

ABA-applied behavior analysis; CBT-cognitive behavioral therapy; IQ-intelligence quotient; N-number; nRCT-nonrandomized controlled trial; RCT-randomized controlled trial

Applicability

Studies of early intensive behavioral and developmental interventions were conducted primarily in preschool and young children (i.e., typically children initially ages 2–7). 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). However, availability and accessibility of the approaches studied are substantially limited in many community based settings. That is, the studies were often either conducted in highly controlled environments (e.g., university supported intervention trials) or the methodology was not well-described (i.e., non-manualized approaches). Even available manualized interventions require high degrees of specialization and training that will likely continue to make translation into common practice difficult.

Studies of parent training interventions and play-based interventions for preschool children, often emphasizing principles of ABA 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. Again the availability of providers capable of translating these programs may be limited in some community settings.

Most studies of social skills interventions targeted elementary school aged children (between 6 and 13 years old) with few studies targeting preschool age children, although such interventions may be important in this younger age group. Most also excluded children with IQ falling outside of the average range and certainly those below 70. Similarly, CBT for commonly associated conditions was targeted toward older children with gross average cognitive abilities and comorbid anxiety disorders.

Limitations of the Review Process

We limited this update to comparative studies and included only those with at least 10 individuals. Thus, we did not include data from pre-post studies or those with a very small number of children. These would include single subject design studies that are helpful for understanding focused questions of short-term efficacy in individual children, and that may be useful for explicating mechanisms of action. These studies are less able to contribute to the body of evidence that we sought on population level and generalizable effects. Users of this review may want to take those studies into account as context when applying our findings. We limited our review to English language studies, not finding evidence that we were missing relevant research in other languages.

Limitations of the Evidence Base

Despite improvements, the existing literature still has significant methodological concerns that in many ways continue to limit the strength of these conclusions. Evidence for the impact of intensive ABA-based interventions on cognitive, language, adaptive skills, and ASD symptoms also highlights important limitations of current treatment modalities. First, even children who demonstrate clinically significant improvements in these areas often continue to display substantial impairment in these same and other areas. Second, not all children receiving intensive ABA-based intervention showed robust improvements in these domains. Thus, although this updated review makes it clearer that early intensive ABA-based intervention improves early impairment related to ASD, it is still challenging to describe the ultimate effect of these improvements in terms of long-term functional and adaptive outcomes on an individual level. Further, although children receiving early intensive developmental and behavioral intervention commonly display substantial improvements, the magnitude of these effects varies across studies and may indicate subgroups showing variable responses to particular interventions. Intervention response is likely moderated by both treatment and child factors. Despite multiple studies of early intensive treatments, intervention approaches still vary substantially, which makes it difficult to tease apart what these unique treatment and child factors may be. Further, researchers have not commonly utilized explicit methodologies or analyses to help elucidate moderation of

treatment response across studies. As such, the current evidence is insufficient, however, to adequately identify and target children most likely to benefit from specific interventions.

Many early intervention studies found that children in all groups improved on cognitive, adaptive, and autism symptom measures regardless of intervention type, although the degree of improvement was often greater in the treatment group. Results were often confounded by nonrandom assignment of participants, including assignment based on child characteristics (such as having the skills necessary to participate in intervention setting) or parental preference. The latter is especially problematic when outcomes are measured by parent report, given some evidence that parental stress influenced parent perceptions of child outcomes. Additionally, in most studies, both enrolled and control/waitlisted children were receiving concomitant interventions, the magnitude of which was inconsistently documented and controlled for in analyses.

A remaining significant challenge to interpreting the early intensive intervention literature relates to how interventions are described and implemented. Although researchers are increasingly attempting to manualize approaches as well as operationalize and measure treatment fidelity, most of the body of literature categorized in this report as "early intensive behavioral and developmental intervention" remains an eclectic grouping. This category of intervention presently groups different treatment approaches (i.e., developmental, intensive behavioral, center based, and combinations), 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 many different outcome measurements over different periods of time (weeks to years). There are intrinsic challenges to manualizing intensive interventions to be delivered over the months and years for a very heterogeneous patient population. However, recent progress toward this end has shown that children will often respond differentially to early intensive approaches.

Few studies directly compared the effects of well-controlled treatment approaches, instead comparing interventions to non-specific "treatment as usual." Additionally, few data on the practical effectiveness or feasibility of these treatments beyond research studies exist, and questions remain about whether reported findings would generalize on a larger scale within communities. Furthermore, the studies conducted have used small samples, drastically different treatment approaches and duration, and different outcome measurements. Similarly, no studies in this category reported harms of intervention in terms of child, family, or system impact.

Although there was a fairly robust evidence base on CBT, the literature lacks head to head comparisons of treatment or controlled comparisons of combinations of treatments despite the fact that most children are undergoing multiple concurrent treatments. Although well designed, the sample sizes are quite modest. Additionally, the CBT approaches were modified for children with ASD and often manualized by the authors themselves.

Research Gaps and Needs

Given the heterogeneity of the expression of ASD within and across children, a critical area for further research is understanding which children are likely to benefit from particular interventions. To date, studies have failed to characterize adequately the characteristics of either interventions or children receiving intervention in a manner that lends towards better understanding of the children experiencing the most positive responses. Further, our understanding of early indicators of treatment response are extremely limited, such that evidence based changes in intervention delivery based on response are not realistic. This is quite important

to parents, providers, and families as they often want to know not only when a treatment is working, but also when they are seeing limited benefit of treatments in order to pursue other treatment options.

Currently, the evidence suggest some children will evidence dramatic improvement, others will display robust improvement in some areas with continued areas of vulnerability in others, and other children will show more moderated response to treatment. It is also unclear how similar groups of children will perform at differing levels of intensity of interventions of different treatment approaches and methods. Research suggests child characteristics, such as baseline cognitive, language, adaptive skill, and ASD symptoms correlate with treatment outcome; however, such correlational data provides limited information in making predictions of what treatments will work best for individual children. Further, intensive comprehensive intervention strategies are often are by their very nature often multi-component, but data on whether specific functional components of the interventions drive effectiveness are currently unavailable. Finally, the intervention research often fails to collect data on pragmatic factors related to family, culture, available resources, and stress that are likely critical to understanding treatment response in a broader real-world context.

A primary methodological concern for the field relates to outcome measurement. Intervention research in the field of ASD has often relied on various and differing ways of marking change which has limited the ability to understand change within and across individual studies.[11] The manner in which outcome in operationalized in many studies is often problematic as well. Quite often outcome is operationalized and studied in terms of change on standardized measures of ability referencing normative populations (i.e., IQ measurement, adaptive behavior scores), which may not necessarily be an appropriate or adequate method for measuring or predicting early treatment response, changes in quality of life, or long-term functional outcomes. Such measurement, while providing data that can be compared to that in typically developing populations, may unfortunately miss important information about changes that are relevant within the ASD population . More simply, it is unclear that measures of cognitive ability, language, and ASD diagnostic symptoms are actually ideal or adequately sensitive methods for measuring frequency, intensity, and impairment in children with ASD. Research on appropriate methods to capture meaningful change will be critical to advance our understanding of behavioral interventions.

Because the treatment process for ASD is typically intensive and often requires highly specific and well-trained individuals to deliver to fidelity, questions of feasibility and accessibility are pertinent but largely understudied. Explicit evaluation of treatments of highest impact in community settings as well as studies explicitly evaluating settings and providers would benefit our ability to understand impact and implementation.

Finally, this literature lacks comparisons of interventions and combinations of interventions (e.g., medical interventions, with behavioral interventions, with educational interventions, with allied health interventions), despite the fact that most children are undergoing multiple concurrent treatments.

Conclusions

In sum, a growing evidence base suggests that behavioral interventions are associated with positive outcomes for children with ASD. Despite improvements in the quality of the included literature, a need remains for studies of interventions across settings and continued improvements in methodologic rigor. Substantial scientific advances are needed to move toward

an enhanced understanding of which interventions are most effective for specific children with ASD.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington DC: American Psychiatric Association, 2013.
2. Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. Pediatrics. 2009 May;123(5):1383-91. PMID: 19403506.
3. Myers SM, Johnson CP. Management of children with autism spectrum disorders. Pediatrics. 2007 Nov;120(5):1162-82. PMID: 17967921.
4. Myers SM. Management of autism spectrum disorders in primary care. Pediatr Ann. 2009 Jan;38(1):42-9. PMID: 19213293.
5. Shattuck PT, Seltzer MM, Greenberg JS, et al. Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. J Autism Dev Disord. 2007 Oct;37(9):1735-47. PMID: 17146700.
6. McGovern CW, Sigman M. Continuity and change from early childhood to adolescence in autism. J Child Psychol Psychiatry. 2005 Apr;46(4):401-8. PMID: 15819649.
7. Fecteau S, Mottron L, Berthiaume C, et al. Developmental changes of autistic symptoms. Autism. 2003 Sep;7(3):255-68. PMID: 14516059.
8. Seltzer MM, Shattuck P, Abbeduto L, et al. Trajectory of development in adolescents and adults with autism. Ment Retard Dev Disabil Res Rev. 2004;10(4):234-47. PMID: 15666341.
9. Warren Z, Veenstra-VanderWeele J, Stone W, Bruzek JL, Nahmias AS, Foss-Feig JH, Jerome RN, Krishnaswami S, Sathe NA, Glasser AM, Surawicz T, McPheeters ML. Therapies for Children With Autism Spectrum Disorders. Comparative Effectiveness Review No. 26. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 11-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.
10. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(13) EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2013. Chapters available at: www.effectivehealthcare.ahrq.gov.
11. Bolte EE, Diehl JJ. Measurement tools and target symptoms/skills used to assess treatment response for individuals with autism spectrum disorder. J Autism Dev Disord. 2013 Nov;43(11):2491-501. PMID: 23479074.

Introduction

Background

Autism Spectrum Disorder (ASD) is marked by persistent impairments in reciprocal social communication and atypical patterns of behavior and interest.[1] Because no medical or biological marker exists for ASD, the diagnosis is behaviorally based. Diagnosis is typically established with a combination of history, observation, and/or formal testing, which may include ASD-specific screening and assessment instruments.[2, 3]

ASD is defined in terms of persistent, significant impairments in social interaction and communication as well as restrictive, repetitive behaviors and activities.[1] Social communication and social interaction features include deficits in social-emotional reciprocity (e.g., deficits in joint attention, atypical social approach and response, conversational challenges, reduced sharing of interest, emotions, and affect), deficits in nonverbal communication (e.g., atypical eye contact, reduced gesture use, limited use of facial expressions in social interactions, challenges understanding nonverbal communication), and deficits in forming and maintaining relationships (e.g., diminished peer interest, challenges joining in play, difficulties adjusting behavior to social context). ASD features of restricted, repetitive patterns of behavior, interests, or activities may include stereotyped motor mannerisms, use of objects, or speech (e.g., simple motor stereotypies, repetitive play, echolalia, and formal or idiosyncratic speech); insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior (e.g., distress at small changes, rigid patterns of thought and behavior, performance of everyday activities in ritualistic manner); intense preoccupation with specific interests (e.g., strong attachment to objects, circumscribed or perseverative topics of interest); and sensory sensitivities or interests (e.g., hyper- or hypo-reactivity to pain and sensory input, sensitivity to noise, visual fascination with objects or movement).[4-6] These symptoms cause impairment across many areas of functioning and are present early in life. However, impairments may not be fully evident until environmental demands exceed children's capacity. They also may be masked by learned compensatory strategies later in life. Many children with ASD may also have intellectual impairment or language impairment, and the disorder may be associated with known medical, genetic, or environmental factors.

Prevalence and Burden of Disease/Illness

The prevalence of ASD in the United States is 11.3 cases per 1,000 (or 1 in 88) children living in the communities surveyed, with rate estimates varying widely by region of the country, sex, and race/ethnicity.[7] Considerably more males (1 in 54) than females (1 in 252) are affected. For some individuals, the core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and maturation[8-10]; however, core deficits typically translate into varying developmental presentations that remain throughout the lifespan.[11] Longitudinal studies indicate that adults with ASD struggle to obtain adaptive independence.[12-16] The estimated costs of medical and nonmedical care (e.g., special education and daycare) for individuals with ASD are high. One study estimates that the total yearly societal per-capita cost of caring for and treating a person with autism in the United States is $3.2 million and about $35 billion for an entire birth cohort of individuals with autism.[17]

Etiology and Risk Factors

ASD has a strong genetic component, with heritability estimated to be between 40 and 90 percent.[18-20] A range of genes is implicated in susceptibility to ASD;[20-22] however, environmental exposures and context also play a role in ASD development and neurogenetic expression.[22, 23] Identification of specific genetic risk variants has been challenging, and many researchers suggest that there are be multiple pathways involved, including prenatal and postnatal insult.[21] Current research[24, 25]suggests that certain metabolic and other maternal conditions (such as diabetes, hypertension, obesity, and influenza infection) during pregnancy may be associated with increased risk of ASD in offspring. Other studies have investigated the role of advanced maternal and paternal age,[26-28] intrapregnancy interval,[29, 30] pesticide exposure,[31] and exposure to mercury and other heavy metals,[32] among other potential risk factors.

In addition to the potential causative genetic and environmental factors described above, being the sibling of another child diagnosed with ASD triples the risk of receiving an ASD diagnosis from 6.7 to 18.7 percent.[33, 34] This risk varies by gender and increases twofold when two or more older siblings have ASD.

Interventions/Treatment

The manifestation and severity of symptoms of ASD differs widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[35-39] that vary by a child's age and developmental status. The goals of treatment for ASD focus on improving core deficits in social communication and social interactions and on minimizing the impact of restricted behaviors, as changing these fundamental deficits may help children develop greater functional skills and independence.[5] Treatment frequently is complicated by symptoms or comorbidities that may warrant targeted intervention. There is no cure for ASD and no global consensus on which intervention is most effective.[38, 40] Individual goals for treatment vary for different children and may include combinations of behavioral therapies, educational therapies, medical and related therapies, and allied health therapies; parents may also pursue complementary and alternative medicine (CAM) therapies.

Behavioral approaches are the cornerstone of treatment approaches for ASD. In 1987, Ivar Lovaas published findings[41] 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 reconceptualized from a largely untreatable disorder[41] to a condition characterized by plasticity and heterogeneity, where there was hope for higher functioning and better outcomes for children receiving appropriate intervention. Subsequent research focused on social communication and behavioral impairments and used both highly structured approaches and natural/developmental approaches that deliver interventions within natural/everyday contexts (Floortime and the Social Communication Emotional Regulation Transactional Support model), some of which integrate approaches (Early Start Denver Model [ESDM]). These types of early and intensive treatment programs typically target behaviors and development more broadly, instead of focusing on a specific behavior of interest.[42] Positive effects seen with these approaches in terms of cognition and language have led to the suggestion that beginning intensive therapy at an earlier age may lead to greater improvements.[40, 42, 43] Recent systematic reviews and meta-analyses have highlighted the potential of early intervention to promote behavioral change.[36-39, 43-52]

Other behavioral approaches include interventions focused on joint attention and play, social skills interventions, and cognitive behavioral therapy and other approaches to ameliorate symptoms commonly associated with ASD such as anger or anxiety.

Chronic management throughout different developmental periods is often required to maximize functional independence and quality of life by minimizing the core ASD features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. Individual goals for treatment vary for different children and may include combinations of therapies. For many individuals core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may see improvements with intervention and over time[8-11]; however, deficits typically remain throughout the lifespan, although developmental expression may vary. There is no cure for ASD and currently no global consensus about which intervention strategies are most effective. Chronic management—often using multiple treatment approaches—may be required to maximize ultimate functional independence and quality of life by minimizing the core ASD features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families.

Scope and Key Questions

The current systematic review updates our comprehensive review of therapies for children with ASD published in 2011.[39] The 2011 review assessed the literature reporting on any interventional approaches (i.e., behavioral, educational, medical, allied health, and CAM) and included more than 150 unique studies, the majority of which were considered of poor quality. Strength of the evidence for most interventions/outcomes was insufficient, with the exception of moderate and high ratings for the effectiveness and harms of the antipsychotics risperidone and aripiprazole. The strength of the evidence was considered low for the effectiveness of early intensive behavioral and developmental intervention. Positive outcomes from an early and intensive behavioral and developmental intervention were noted in cognitive performance, language skills, and adaptive behavior when the intervention was delivered over substantial intervals of time (i.e., 1–2 years) but at the time, a limited body of comparative evidence led to a low strength of evidence for these effects. Variability in response to such approaches was large, with subgroups of children who demonstrated a more moderated response. The ability to describe and predict these subgroups was limited.

Since the publication of the initial review in 2011, a sizable body of research has been published on behavioral interventions. Additional studies of these interventions have the potential to alter the low and insufficient strength of evidence reported in the original review and potentially affect treatment recommendations.

Key Questions

As noted, we focused this review on behavioral treatments for children ages 0-12 with ASD or very young children at risk of a diagnosis of ASD. We have synthesized evidence in the published literature to address these key questions (KQ):

KQ1: Among children ages 2-12 with ASD, what are the short and long-term effects of available behavioral 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 behavioral 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 behavioral treatment as driving outcomes, either within a single treatment or across treatments?

KQ7: What evidence supports the use of a specific behavioral 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?

Organization of This Report

The report describes our review 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 the evidence table and compiling evidence. We also describe the approach to grading of the quality of the literature and to evaluating the strength of the body of evidence.

The results section synthesizes the findings by category of behavioral intervention (see Categorization of Interventions below). We report the number of comparative studies fully described in the 2011 review, the number and type identified for the current review, and any overlap of studies (i.e., those reporting followup data) between the prior and this current review. We make our conclusions and assess the strength of evidence on the cumulative, comparative evidence across the original report and update. [39]

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 also integrate discussion of sub-questions within that for each key question because there was not adequate distinction in the literature to address them separately. Full details of the results of studies addressed in the prior review can be found in that report.[39]

The report's discussion section expands on methodologic considerations relevant to each key question and outlines the strength of the evidence for key outcomes, current state of the literature and challenges for future research on ASD. The report includes a number of appendixes to provide further detail on our methods and the studies assessed. The appendixes are as follows:

- Appendix A: Search Strategies and Results
- Appendix B: Screening and Quality Assessment Forms
- Appendix C: Evidence Tables
- Appendix D: Quality of the Literature
- Appendix E: Excluded Studies
- Appendix F: Characteristics and Outcomes of Studies of Early Intensive Behavioral and Developmental Interventions
- Appendix G: Applicability Summary Tables.

A list of abbreviations and acronyms used in the report follows the References section.

Categorization of Interventions

In line with the 2011 review, we define behavioral interventions as follows: behavioral interventions include early intensive behavioral and developmental interventions, social skills interventions, parent training, play/interaction-focused interventions, interventions targeting symptoms commonly associated with ASD such as anxiety, and other general behavioral approaches.

Early intensive behavioral and developmental interventions. We adopted a similar approach to the operationalization of the early intensive behavioral and developmental intervention category as Rogers and Vismara in their review of "comprehensive" evidence-based treatments for early ASD.[43] Interventions in this category all have their basis in or draw from principles of ABA, with differences in methods and setting. ABA is an umbrella term describing principles and techniques used to assess, treat, and prevent challenging behaviors and the promotion of new, desired 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 before being specifically applied to the study and treatment of ASD.

We include in this category two intensive interventions that have published manuals to facilitate replication: the University of California, Los Angeles (UCLA)/Lovaas model and the Early Start Denver Model (ESDM). These two interventions have several key differences in their theoretical frameworks and in how they are implemented, although they share substantial similarity in the frequent use of high-intensity (many hours per week, one-on-one) instruction using ABA techniques. They are described together here because of these similarities. We note, however, that the UCLA/Lovaas method relies heavily on one-on-one therapy sessions during which a trained therapist uses discrete trial teaching with a child to practice target skills, while ESDM blends ABA principles with developmental and relationship-based approaches for young children.

The other treatment approaches in this category also incorporate ABA principles and may be intensive in nature; often, however, they have not been documented in a manual. We have classified these approaches broadly as UCLA/Lovaas based given their similarity in approach to the Lovaas model. A third particular set of interventions included in this category are those using principles of ABA to focus on key pivotal or foundational skills and behaviors (such as

motivation to communicate or initiation of communication), rather than global improvements. These approaches often emphasize parent training as a modality for treatment delivery (e.g., Pivotal Response Training, Hanen More than Words, social pragmatic intervention, etc.) and may focus on specific behaviors such as initiating or organizing activity or on core social communication skills. Because they emphasize early training of parents of young children, they will be reviewed in this category.

Social skills interventions. Social skills interventions focus on facilitating social interactions and may include peer training and social stories.

Play/interaction-focused interventions. These approaches use interactions between children and parents or researchers to affect outcomes such as imitation or joint attention skills or the ability of the child to engage in symbolic play.

Interventions focused on behaviors commonly associated with ASD. These approaches attempt to ameliorate symptoms such as anger or anxiety, often present in children with ASD, using techniques such as Cognitive Behavioral Therapy (CBT) and parent training focused on challenging behaviors.

Additional behavioral interventions. We will categorize approaches not cleanly fitting into the behavioral categories above in this group.

Methods

Topic Development and Refinement

The 2011 report was nominated by Autism Speaks in a public process. We drafted the initial key questions and analytic framework and refined them with input from key informants and a focus group of family members of children with autism spectrum disorder (ASD). After review from the Agency for Healthcare Research and Quality (AHRQ), the questions and framework were posted to a public Web site. After reviewing the public commentary, we drafted final key questions and submitted them to AHRQ for review. The need for an update of that report was documented through an ongoing update assessment project at AHRQ.

For the current update, we identified technical experts on the topic of ASD in children to provide input during the project. Technical Expert Panel (TEP) members represented the clinical and research communities from a range of perspectives. TEP members included both researchers and clinicians with expertise in behavioral, social, and psychological issues. To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and key questions to ensure that they continued to represent important decisional dilemmas;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Ensure that we had captured seminal studies addressing interventions for children with ASD.

After discussions with the TEP and our initial scan of the literature, we retained all of the Key Questions (KQ) from the earlier review in the current report, modifying them slightly to reflect a focus on behavioral interventions. The protocol for the current update is available on the AHRQ Effective Health Care web site.

Role of the AHRQ Task Order Officer

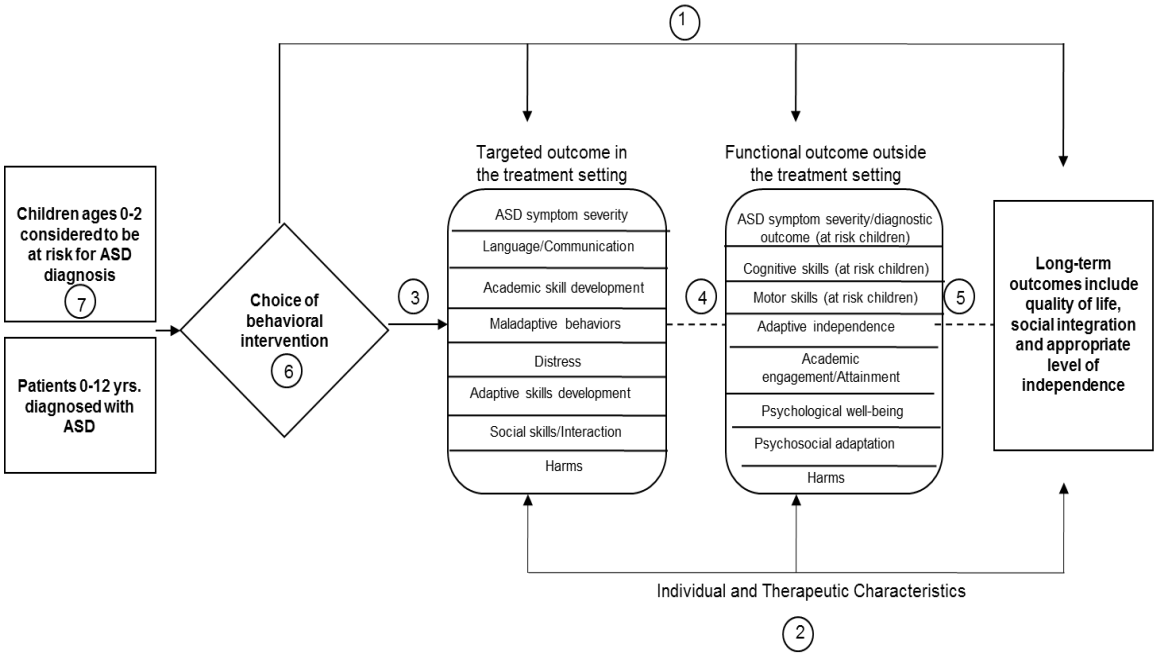
The Task Order Officer (TOO) was responsible for overseeing all aspects of this project. The TOO helped to develop a common understanding among all parties involved in the project, resolved questions and ambiguities, and addressed our queries regarding the scope and processes of the project. The TOO reviewed the report for consistency, clarity, and to ensure that it conforms to AHRQ standards.

Analytic Framework

Figure 1 summarizes the process by which families of children with ASD make and modify treatment choices. Circled numbers indicate the KQs, and their placement indicates the points in the treatment process where they are likely to arise. This update focuses on behavioral interventions for children with ASD or considered to be at risk for ASD. The population of interest is patients 0–12 years diagnosed with ASD. Individuals engage in behavioral interventions, which may lead to specific outcomes (KQ 1). Outcomes may be modified by characteristics of the child/family or of the intervention (KQ 2). KQ 3 involves identifiable changes early in the treatment process that may affect outcomes. KQ 4 involves the relationship between targeted outcomes in the treatment setting and functional outcomes outside the treatment setting. KQ 5 involves generalization of interventions to other contexts, and KQ 6 addresses components of treatments that may drive outcomes, the “active ingredients” of

treatments. KQ 7 addresses treatments for very young children considered to be at risk for ASD. Target outcomes in the treatment setting include ASD symptom severity, language/ communication, academic skill development, maladaptive behaviors, distress, adaptive skills development, and social skills/interaction. Functional outcomes outside the treatment setting include adaptive independence, academic engagement/attainment, psychological well-being, and psychosocial adaptation; for children considered to be at risk, the outcomes include changes in ASD symptom severity or diagnostic outcome, motor skills, and cognitive skills. Long-term outcomes include quality of life, social integration, and appropriate level of independence. Harms of intervention are also considered.

Figure 1. Analytic framework for behavioral interventions for children with ASD



ASD=autism spectrum disorder; KQ=key question.

Literature Search Strategy

Databases

A librarian employed search strategies provided in Appendix A to retrieve research on interventions for children with ASD. Our primary literature search employed three databases: MEDLINE® via the PubMed interface, PsycINFO® (psychology and psychiatry literature), and the Educational Resources Information Clearinghouse. Our search strategies used a combination of subject heading terms appropriate for each database and key words relevant to ASD (e.g., autism, Asperger). We limited searches to the English language and literature published since the development of the 2011 review.

We also manually searched the reference lists of included studies and of recent narrative and systematic reviews and meta-analyses addressing ASD. We also invited TEP members to provide additional citations.

Grey Literature and Hand Searching

As the review focuses on behavioral interventions, we did not search for regulatory information. As noted, we hand searched the reference lists of included studies and recent reviews.

Search Terms

Controlled vocabulary terms served as the foundation of our search in each database (e.g., MEDLINE vocabulary terms including autistic disorder, child development disorders, pervasive), complemented by additional keyword phrases (e.g., Asperger, autism). We also limited searches to items published in English. Our searches were executed in July 2013. Appendix A provides our search terms and the yield from each database. We imported all citations into an electronic database.

Process for Study Selection

Inclusion and Exclusion Criteria

We developed criteria for inclusion and exclusion based on the patient populations, interventions, outcome measures, and types of evidence specified in the key questions and in consultation with the TEP. Table 1 summarizes criteria.

Table 1. Inclusion criteria

Category	Criteria
Study population	Children ages 0-12 with ASD or 0-2 considered to be at risk for ASD based on sibling status or early developmental/behavioral vulnerabilities highly suspicious of ASD
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs RCTs, prospective and retrospective cohort studies, and nonrandomized controlled trials 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 and ≥ 10 participants with ASD Studies must address one or more of the following for ASD: -Behavioral treatment modality -Predictors of treatment outcomes -Generalization of treatment outcomes to other contexts -Drivers of treatment outcomes Relevant outcomes must be able to be abstracted from data in the papers Data must be presented in the aggregate (vs. individual participant data)

ASD=autism spectrum disorder; RCTs=randomized controlled trial.

Study Population

Studies needed to provide adequate information to ensure that participants fell within the target age range. For studies with populations including individuals with ASD in our target range and over age 12, we retained the study if we could infer that at least 80 percent of the study participants were in the 0 to 12 age range or if the mean age of participants did not exceed 12 years and 11 months. Similarly, for studies including individuals with ASD and those with other

developmental disabilities, we retained the study if we could isolate data on those participants with ASD.

Sample Size

We included studies with at least 10 individuals with ASD between the ages of 0 to 12 years. Our goal was to identify and review the best evidence for assessing the efficacy and effectiveness of therapies for children with ASD, with an eye toward utility in the treatment setting. Interventions to address ASD are frequently behavioral in nature and highly intensive. They are also frequently adapted to be targeted to specific study participants given the significant heterogeneity of individuals with ASD. In part because this makes behavioral research quite complex and intensive, study sizes tend to be very small. A cutoff sample size of 10 provides a balance, allowing us to review and comment on adequate literature for the review but with studies large enough to suggest effects of the interventions.

With the assistance of our technical experts, we selected a minimum sample size of 10 in order to maximize our ability to describe the state of the current literature, while balancing the need to identify studies that could be used to assess treatment effectiveness.

Study Design

We accepted any comparative study designs; that is any study that included both a treatment/intervention and a control group. Control participants could receive an alternate intervention, no intervention/waitlist, or placebo.

Outcomes

We assessed outcomes in the broad areas of symptom severity, cognitive skills, motor skills, adaptive behavior, language/communication, maladaptive behavior, distress, social skills, and academic attainment. We considered intermediate outcomes as those that occur directly as a result of the intervention and that may also have longer term implications for the ultimate, functional outcomes that are the long-term goal of therapies. We also assessed the harms of interventions, defined by the AHRQ Effective Health Care program as the totality of adverse consequences of an intervention.[53]

Language

We focused the review on studies published in English. In the opinion of our content experts, most research on ASD is published in English regardless of the native language of the investigators or country of publication.

Screening of Studies

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. 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 for full text assessment.

Two reviewers independently assessed the full text of each included study using a standardized form (Appendix B) that included questions stemming from our inclusion/exclusion criteria. Disagreements between reviewers were resolved by a third-party adjudicator. The group

of abstract and full text reviewers included expert clinicians and researchers and health services researchers.

Data Extraction and Data Management

The staff members and clinical experts who conducted this review jointly developed the evidence tables, which were used to extract data from the studies. We used table categories and parameters as outlined in the 2011 review. Tables aim 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, and baseline and outcome data on constructs of interest.

All team members shared the task of initially entering information into the evidence table. Another member of the team also independently reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The full research team met regularly during the article extraction period and discussed issues related to data extraction (e.g., optimal level of detail in the description of the intervention). In addition to outcomes related to treatment effectiveness and modifiers of effects, we extracted 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 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. For those studies reported in the 2011 review and with follow-up data reported here, the evidence table for the original studies can be found in the 2011 report.[39]

Individual Study Quality Assessment

We used a components approach to assessing the quality of individual studies, developed for the 2011 review and following methods outlined in the AHRQ Effective Health Care program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[54] We assessed the quality of studies in the domains below using specific questions to evaluate a study's conduct. We rated each domain individually and combined them for an overall quality level as described below and in Appendix D. Three levels were possible: good, fair, and poor (Table 2).

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?

Diagnostic 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/or ADOS assessments.
   - B. A combination of a DSM-IV clinical diagnosis with one other assessment tool; or the ADOS assessment in combination with one other assessment tool.
   - C. Either a clinical DSM-IV-based diagnosis alone or the ADOS assessment alone.

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

Participant ascertainment

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?

Intervention characteristics

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?

Outcomes measurement

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?

Statistical analysis

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?

Table 2. Description of study quality levels

Quality Level	Description
Good	Good studies are considered to have the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to treatments; has a low dropout rate; and uses appropriate means to prevent bias; measure outcomes; analyze and report results.
Fair	Fair studies are susceptible to some bias, but probably not sufficient to invalidate the results. A study may be missing information, making it difficult to assess limitations and potential problems. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	Poor studies are subject to significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Determining Quality Levels

We assessed each domain described above individually and considered the individual ratings to determine an overall quality assessment of good, fair, or poor. We required that studies receive

positive scores questions related to study design and diagnostic approach to be considered good quality. Scores were calculated first by domain and then summed and weighted as described in Table 4 to determine overall study quality. Studies could receive up to two points on the domains of study design, diagnostic approach, participant ascertainment, and intervention, and up to one point on the domains of outcome measurement and statistical analysis.

Table 3. 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 quality
• 6/10 points, including at least a + on intervention	Fair quality
• 5/10 points or less	Poor quality

Data Synthesis

We summarized studies qualitatively using evidence tables and descriptive synthesis.

Grading the Body of Evidence for Each Key Question

The assessment of the literature is done by considering both the observed effectiveness of interventions and the confidence that we have in the stability of those effects in the face of future research. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence, and it can be regarded as insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, both in terms of quantity and quality, as well as the degree to which the entire body of current research provides a consistent and precise estimate of effect. Interventions that have demonstrated benefit in a small number of studies but have not yet been replicated using the most rigorous study designs will therefore have insufficient or low strength of evidence to describe the body of research. Future research may find that the intervention is either effective or ineffective.

Methods for applying strength of evidence assessments are established in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[54] and are based on consideration of five domains (Table 4): study limitations, consistency in direction of the effect, directness in measuring intended outcomes, precision of effect, and reporting bias. Strength of evidence is assessed separately for major intervention-outcome pairs and incorporates data from the entire body of reviewed evidence on behavioral interventions (i.e., comparative studies reported in the 2011 review and studies reported in the current review). We required at least three fair studies to be available to assign a low strength of evidence rather than considering it to be insufficient. We required at least one good study for moderate strength of evidence and two good studies for high strength of evidence. In addition, to be considered "moderate" or higher, intervention-outcome pairs needed a positive response on two out of the three domains other than risk of bias.

Once we had established the maximum strength of evidence possible based upon these criteria, we assessed the number of studies and range of study designs for a given intervention-outcome pair, and downgraded the rating when the cumulative evidence was not sufficient to justify the higher rating. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates

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

Table 4. Domains used to assess strength of evidence[a]

Domain	Explanation
Study Limitations	Degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through study design and study conduct.
Consistency	Degree to which included studies find either the same direction or similar magnitude of effect. Assessed through two main elements: • Direction of effect: Effect sizes have the same sign (that is, are on the same side of no effect or a minimally important difference). • Magnitude of effect: The range of effect sizes is similar.
Directness	Extent to which evidence links interventions directly to a health outcome of specific importance for the review, and for comparative studies, whether the comparisons are based on head-to-head studies. Evidence may be indirect in several situations such as: • Outcome being graded is considered intermediate in a review that is focused on clinical health outcomes (such as morbidity, mortality). • Data do not come from head-to-head comparisons but rather from two or more bodies of evidence to compare. • Data are available only for proxy respondents instead of directly from patients for situations in which patients are capable of self-reporting and self-report is more reliable.
Precision	Degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events. A body of evidence will generally be imprecise if the optimal information size (OIS) is not met. OIS refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered.
Reporting bias	Degree of selective publishing or reporting of research findings based on the favorability of direction or magnitude of effect.

[a] Excerpted from Berkman et al. 2013[55]

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/treatment setting but are hoped to change behavior overall). Our assessment of applicability included determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category.

Peer Review and Public Commentary

Researchers and clinicians with expertise in behavioral, medical, social, psychological and educational issues and individuals representing stakeholder and user communities will be invited to provide external peer review of this report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and documenting changes and revisions to the report in a disposition of comments report that will be made available 3 months after AHRQ posts the final review on the AHRQ Web site.

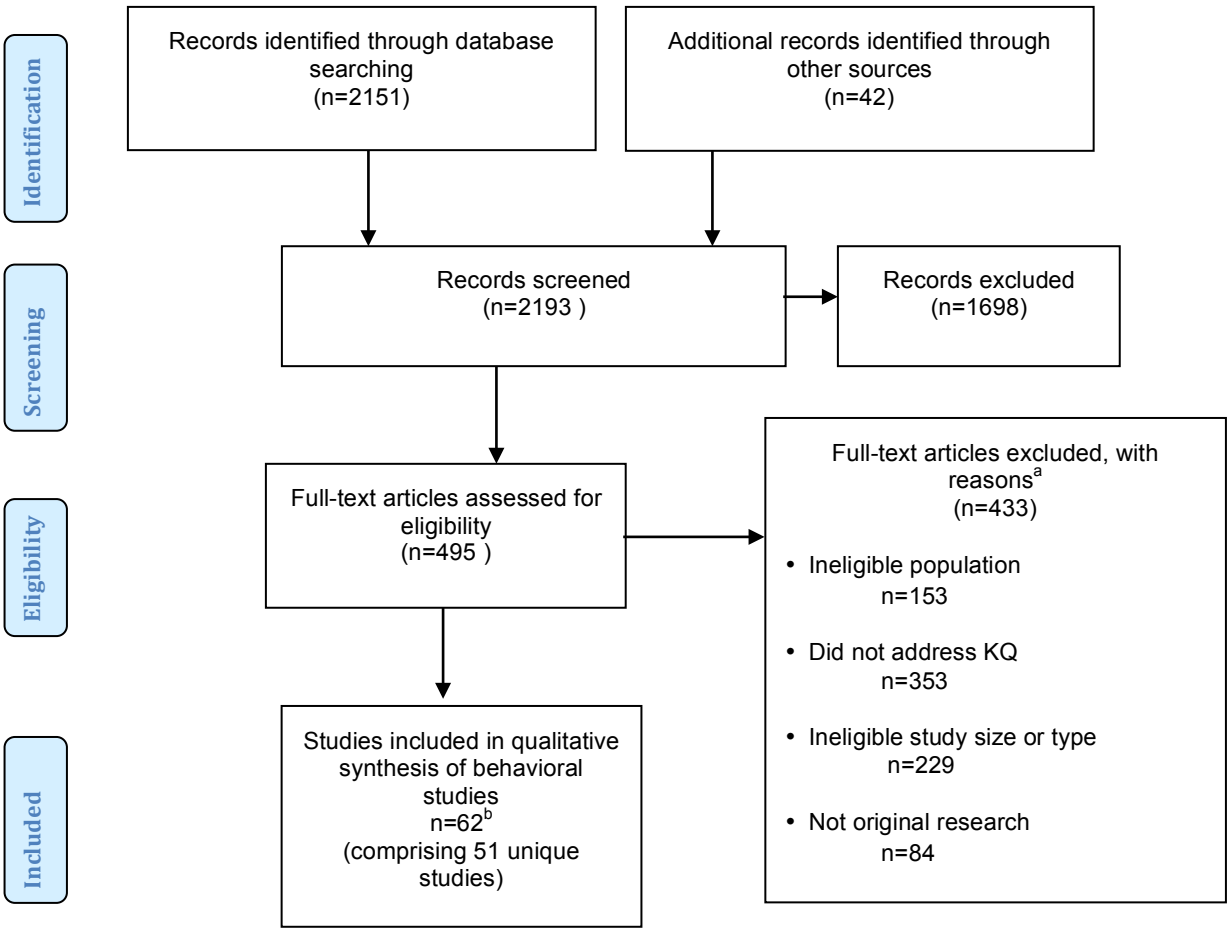
Results

Results of Literature Searches and Description of Included Studies

Article Selection

We identified 2193 citations and abstracts (Figure 2). We excluded 1698 studies at abstract review and assessed the full text of 495 studies. Among these, 62 publications, comprising 51 unique studies, met our criteria. Seven of these studies report followup data to papers included in the 2011 review of therapies for children with autism spectrum disorder (ASD). The 51 included studies comprise 37 randomized controlled trials (RCTs) and 14 nonrandomized trials or cohort studies. Table 5 outlines study characteristics. Appendix E includes a list of all studies excluded at the abstract and full-text review stages.

Figure 2. Disposition of studies identified for this review



[a] Numbers do not tally as studies could be excluded for multiple reasons.
[b] 7 studies among these include followup data from studies reported in the 2011 review.
KQ=key question; n=number.

Table 5. Overview of included studies

Characteristic	RCTs	nRCTs	Prospective Cohort Studies	Retrospective Cohort Studies	Total Literature
	(n=37)	(n=3)	(n=10)	(n=1)	(n=51)
Intervention					
Early intensive behavioral and developmental	10	1	9	1	21
Social skills	9	1	0	0	10
Play-/interaction-based	8	0	1	0	9
Interventions targeting associated behaviors	7	0	0	0	7
Other	3	1	0	0	4
Treatment duration					
<1 month	2	0	0	0	2
≥1 to ≤3 months	21	2	2	0	25
>3 to ≤6 months	7	0	1	0	8
>6 to ≤12 months	5	1	4	1	11
>12 months	2	0	3	0	5
Final followup after end of treatment					
Immediately post-treatment	23	2	8	0	33
≥1 to ≤3 months	7	0	1	0	8
>3 to ≤6 months	3	0	0	0	3
>6 to ≤12 months	1	1	0	0	2
>12 months	3	0	1	0	4
Not reported/unclear	0	0	0	1	1
Study population					
U.S./Canada	24	0	2	1	27
Europe	7	2	6	0	15
Asia	3	0	0	0	3
Other	3	1	2	0	6
Total N participants	1939	69	628	142	2778

N-number; nRCT-nonrandomized controlled trial; RCT-randomized controlled trial

KQ1. Effects of Behavioral Interventions on Core and Commonly Associated Symptoms in Children With ASD

A wide range of interventions can be classified as behavioral. For the 2011 review and this update, we included studies of early intensive behavioral and developmental interventions, which comprised University of California, Los Angeles (UCLA)/Lovaas-based approaches, the Early Start Denver Model (ESDM), and parent training approaches incorporating principles of Applied Behavior Analysis (ABA) to improve outcomes among young children with ASD; social skills

interventions; focal play-based /interaction-based interventions; behavioral interventions focused on commonly associated behaviors; and a small group of other behavioral interventions assessing other interventions in core/associated areas (e.g., sleep workshops).

Early Intensive Behavioral and Developmental Interventions

Key Points

- Of the 21 studies addressing early intensive behavioral and developmental interventions, six were good, 12 were fair, and three were poor quality.
- Many studies used parent-report measures of adaptive and autism symptom-related outcomes, which may be confounded by parental stress, parental involvement in treatment protocols, and nonrandom assignment based upon parental treatment preferences.
- All studies of ABA-based interventions compared a minimum of two treatment groups. No study included a control group that was not receiving some type of intervention (including school enrollment or eclectic community-based therapies, such as medication or occupational therapy), although some limited the number of behaviorally based treatment hours that control participants could receive.
- Studies with parent training components reported improvements in language with inconsistent results for other outcomes.
- No studies reported harms.

Overview of the Literature

In the 2011 review, we identified 17 comparative studies[56-74] (described in 19 papers), of which six were RCTs (two good quality,[72, 74] four fair[56, 68, 70, 71]), five were nonrandomized trials (four fair quality,[63-67, 73] one poor[69]), four were prospective cohort studies (three fair[59, 60, 62] and one poor quality[61]), and two were poor quality retrospective cohort studies.[57, 58] For the current review we identified 21 comparative studies (reported in 31 publications) meeting our inclusion criteria and evaluating either ABA-based early intervention approaches[72, 75-89] or approaches integrating parent training components).[71, 90-103] Four of these studies (published in multiple papers) report followup data for studies reported in the 2011 review.[71, 72, 78, 79, 84-89, 103] Additionally, one study in the current report[93] may include some participants reported in studies in the 2011 review.[104, 105]

ABA-based approaches. Nine studies (reported in 16 publications) assessed ABA-based early intensive behavioral and developmental intervention (Table 6).[72, 75-87, 89, 106] Studies included two RCTs conducted in the United States;[72, 83, 84] one non-randomized controlled trial conducted in Europe;[75] three European,[76-78] one U.S.-based,[82] and one Israeli[80] prospective cohort study; and one Canadian retrospective cohort study that reported on segments of the same population in multiple publications.[85-89] Five studies compared ABA-based approaches to care-as-usual community therapies[72, 77, 78, 80, 84, 85] and four to preschool-based programs.[75, 76, 82, 83] Mean participant age ranged from 15-72 months. Treatment duration ranged from 6 to 24 months. We rated one study as good, seven studies as fair, and one study as poor.

Parent training. We identified 12 studies (reported in 15 publications) of early intervention with parent training components (Table 7).[71, 90-103] Studies included three European[93, 95, 99, 100] and one Australian[98] prospective cohort studies; three RCTs conducted in the United States,[91, 96, 101, 102] two (including one crossover) in Asia,[90, 97] one in Australia,[94] and two (one with suboptimal randomization) in Europe.[71, 92, 103] Five studies compared parent training to treatment as usual

(community-based intervention).[71, 84, 90, 91, 96, 100, 103] Five compared ABA-based parent training to other parent-training paradigms[95, 98, 101, 102] or multiple other interventions,[93, 94] and the comparison arm in one study received no specific intervention.[97] Mean participant age ranged from 17.8 to 66 months. Treatment duration ranged from 12 weeks to 2 years. We rated five studies as good, five studies as fair, and two studies as poor.

Detailed Analysis

ABA-based Approaches

One fair quality RCT examined the use of the Learning Experiences and Alternative Program for Preschoolers and Their Parents (LEAP) protocol in preschool classrooms in the United States.[83] The study compared 27 classrooms (n children=177; mean age: 50.1 months ± 4.6 months) with teachers trained in the full LEAP curriculum (including peer mediated social skills, incidental teaching, pivotal response training, the Picture Exchange Communication System (PECS), and positive behavior support) to 23 classrooms (n children=117; mean age: 50.7 months ± 4.2 months) where teachers received the LEAP manual but no formal training. Both groups received an average of 17 hours per week of intervention over two years. Relative to the manuals-only group, children in the full LEAP training classrooms showed significant ($p < .05$) improvement on Childhood Autism Rating Scale (CARS) ratings, language, cognitive, and social skills measures. The students of teachers rated as having better intervention fidelity showed better outcomes on all measures.

Five additional studies examined the use of school-based ABA programs (one fair quality nonrandomized controlled trial and four fair quality prospective cohort studies.[76, 77, 80-82] All five compared standard special education preschool curriculums to special education preschools with some sort of enhanced intervention modality, including general ABA,[80, 81] individual UCLA/Lovaas-based behavioral intervention,[75, 77] Treatment and Education of Autistic and Communication related handicapped Children (TEACCH)- or LEAP- programs,[82] and a mix of behaviorally-based operant conditioning techniques.[76] Mean treatment intensity ranged from 13.8-28.38 hours per week, with length of enrollment varying from 8-24 months. Mean child ages ranged from 25.1-53.5 months.

The effects of enhanced school-based interventions relative to standard special education preschool curricula were mixed. Some studies[75-77] found that the enhanced intervention groups showed greater gains in cognitive outcomes and parent-reported adaptive skills. Other studies found that children in all groups improved on cognitive, adaptive, and autism symptom measures[75, 80-82] regardless of intervention type, although in some cases treatment groups showed greater improvements.[75] Others found declines in both groups on standardized scores of motor skills.[80, 81] Intervention efficacy was associated with baseline cognitive scores in one study of TEACCH classrooms,[82] with lower baseline cognitive scores associated with more improvement. Lower baseline autism severity was associated with parent-reported cognitive and adaptive growth for children who received eclectic vs. ABA intervention, but not with standardized test scores.[80, 81] Additional UCLA/Lovaas-style intervention over-and-above classroom involvement was associated with reduced autism symptoms as rated by clinicians on the CARS[77] but not as rated by parents using the Scale of Pervasive Developmental Disorder in Mentally Retarded Persons.[75] Where examined, total hours of intervention per week were not associated with cognitive or adaptive outcomes, although hours were similar across intervention groups within each study (e.g., comparing half-day programs to other half-day programs).

Three studies compared ABA-based early intervention to eclectic treatment as usual.[72, 78, 84, 85] One good quality RCT compared ESDM to community-based interventions.[72, 84] It randomized children into two groups based on gender and IQ. For two years, 24 children in the ESDM arm (mean age: 23.9 ± 4.0, mean IQ: 61.0 ± 9.2) received 1:1 therapist-delivered manualized intervention (mean of 15.2 ± 1.4 hours/week) as well as parent-delivered treatment (mean 16.3 ± 6.2 hours/week). The comparison group of 21 children (mean age: 23.1 ± 3.9, mean IQ: 59.4 ± 8.6) received individual (mean 9.1 hours/week) and group (mean 9.3 hours/week) therapies, including speech-language therapy, occupational therapy, and developmental preschool enrollment. After one year of treatment, The ESDM group showed significantly greater improvement in IQ but not adaptive behavior. After two years of treatment, the ESDM group continued to show significantly more IQ improvement as well as receptive and expressive language. Both groups improved in all domains of adaptive behavior but socialization, with greater improvements in the ESDM group. Neither group showed significant differences in Autism Diagnostic Observation Schedule (ADOS) severity scores or repetitive behavior, although the ESDM group demonstrated a diagnostic shift toward a milder diagnosis (PDD-NOS) at follow-up. Electroencephalography (EEG) measures of engagement and cognitive processing for children in the ESDM group with usable data were comparable to typically developing children.

A fair quality Canadian retrospective cohort study[85-89] matched children receiving a large-scale, publicly funded, community-based early intensive intervention program that incorporated ABA, discrete trial training, and naturalistic approaches (n=61, mean age=42.93 ± 11.53 months) to waitlisted children receiving care-as-usual (n=61, mean age=42.79 ± 10.51 months). The intervention group received treatment (mean 25.81 ± 3.44 hours/week) conducted by trained instructor therapists in specialized centers, preschools, and the home environment. The control group received a mean of 17.9 ± 12.3 hours/week of school-based services and <10 hours/week of behavioral intervention conducted by community-based interventionists in community settings. The approaches included low-intensity ABA, speech and occupational therapy, and behavioral consultation. Children in the treatment arm were enrolled in treatment longer (mean=27.84 ± 8.11 months) than children in the waitlist group (mean=17.01 ± 2.81months), and analyses controlled for this difference.

ASD severity improved for the treatment group compared with control, as did Vineland composite standard and ratio scores and IQ estimates (p values ≤ .033, effect sizes ranging from 0.53 to 0.83). Although treatment group participants had cognitive scores an average of 19 points higher than controls at follow-up, this should be interpreted with caution due to a lack of baseline cognitive data. Outcomes were related to age at enrollment, treatment duration, and higher baseline adaptive scores, with duration becoming nonsignificant after accounting for group membership (correlation of duration, group=.57, $p < .01$). A significant interaction emerged between age at enrollment and group membership, with younger starting age influencing outcomes for the treatment group but not control. Analyses including participants in the cohort study and additional participants found that younger age at intake, higher initial developmental levels[89] and treatment intensity[87, 89] were related to treatment outcomes.

Finally, a poor quality UK study[78, 79] compared the long-term effects (2 years post-treatment) of 1:1 home-based early intervention (both university-provided and privately-provided) to community-based treatment-as-usual, including PECS, TEACCH, and medication. The early intervention group included 23 children (mean age=35.7 ± 4 months; mean IQ=61.43 ± 16.43 months), and the community-based group included 18 (mean age=38.4 ± 4.4 months; mean

IQ=62.33 ± 16.64) at the two-year followup, with children in the community-based group significantly older at the start of treatment ($p < .05$). For 24 months, children in the early intervention group received an average of 25.6 hours/week of ABA-based intervention using discrete trial training in the home environment, whereas children in the community-based arm received an unspecified amount of eclectic treatment. After 24 months of intervention, IQ, mental age, and language comprehension/expression improved significantly for the ABA group versus community-based ($p \leq .05$; effect size for IQ change=0.77). At the two year follow-up, IQ gains were only maintained for children who received privately-provided ABA-based intervention. IQ remained stable for children in the community-based group and significantly declined for children who received university-provided intervention (effect size=.49). This result is confounded by nonrandom assignment and the fact that at baseline, the university-based group had higher levels of autism symptoms, lower levels of adaptive behavior, and fewer total intervention hours.

Table 6. Key outcomes of ABA-based early intervention studies

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Months ± SD IQ, Mean ± SD	Key Outcomes
Peters-Scheffer et al.2010[75] Netherlands **G1:** Specialized preschool +UCLA/ Lovaas-based intervention, 12/12 **G2:** Specialized preschool, 22/22 Quality: Fair	**G1:** 53.5 ± 5.52 **G2:** 52.95 ± 11.14 **G1:** 47.00 ± 10.33 **G2:** 45.73 ± 15.99	• Both groups improved over time on cognitive and adaptive measures; G1 improved significantly compared with G2 on IQ/developmental age and Vineland composite, communication, daily living, and socialization domains (all p≤.02) • G2 had greater emotional and behavioral problem scores at baseline vs. G1 (p<.05), changes in scores not significant for either group over time • Decreases in symptom severity not significant between groups
Strain et al. 2011[83] US **G1**: LEAP program with coaching and training, 28 classrooms (27 analyzed)/177 children **G2**: LEAP intervention manuals only, 28 classrooms (23 analyzed)/117 children Quality: Fair	**G1:** 50.1 ± 4.6 **G2:** 50.7 ± 4.2 **G1:** 59.6 ± 6.9 **G2:** 63.2 ± 6.6	• Significant gains on CARS, language, cognitive, and social skills measures for G1 vs. G2 (P<.05) • G1 improved by 18.5 points compared with 9.4 for G2 on the Preschool Language Scale (effect size difference=0.92, p<.01) • G1 improved by 28.6 points compared with 12 for G2 on socials skills rating (effect size difference=1.22, p<.01) • Greater intervention fidelity associated with better outcomes on all measures
Boyd et al. 2013[82] US **G1:** TEACCH preschools, 85/81 **G2:** LEAP preschools, 54/48 **G3:** Non-model specific preschools, 59/56 Quality: Fair	G1: 48 ± 6.84 G2: 47.52 ± 8.4 G3: 48.84 ± 7.68 NR	• Groups differed at baseline on autism characteristics and severity (p=.0013), communication (p<.001), parent-rated reciprocal social interaction (p=.0241) and fine motor (p=.0066) composite scores • All groups showed significant change over time on the autism characteristics and severity, fine motor, and communication composites (p values ≤.05); G1 and G2 improved on teacher-rated reciprocal social interaction (p≤.05). G1 improved on parent-rated reciprocal social interaction (p<.05) • No significant differences among groups on any measure at followup • Children with higher Mullen scores made fewer gains in G1; children with high Preschool Language Scale scores at baseline had higher communication and autism characteristics and severity composite scores in G1 • Females in G2 had smaller communication gains , although few females in study overall (n=33)

Table 6. Key outcomes of ABA-based early intervention studies, continued

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Months ± SD IQ, Mean ± SD	Key Outcomes
Eldevik et al. 2012[76] Norway **G1:** Preschool-based early intensive intervention, 31/31 **G2:** Usual care preschool, 12/12 Quality: Fair	**G1:** 42.2 ± 9.0 **G2:** 46.2 ± 12.4 **G1:** 51.6 ± 16.9 **G2:** 51.7 ± 18.1	• Greater gains in cognitive outcomes (p=.004) and overall adaptive behavior (p=.036) , Vineland communication (p=.034) and socialization (p=.008) for G1 vs. G2; no significant differences in Vineland daily living skills between groups • Effect size for change in IQ=1.03 (95% CI: .34 to 1.72) and for change in overall adaptive behavior=.73 (95% CI: .05 to 1.36) • Baseline age and PDD-NOS or Asperger diagnosis correlated with larger gains in overall adaptive behavior, communication, and daily living skills; baseline IQ positively correlated with Vineland socialization gains
Eikeseth et al. 2012[77] Norway/Sweden **G1:** Early intensive intervention, 35 / 13-15 depending on outcome **G2:** Standard care , 24 / NR Quality: Fair	**G1:** 3.9 ± 0.9 years **G2:** 4.4 ± 1.2 years Vineland age equivalent: **G1:** 1.9 ± 0.9 **G2:** 2.1 ± 0.8	• G1 scored significantly higher on all Vineland scales as compared withG2 (p<0.05) with an effect size of Total (composite)=0.92, Communication=1.08, ADL=0.71, Socialization=0.75,Motor=0.70, and Learning rate=0.97 • G1: CARS scores continued to decrease significantly during the second year of treatment (from 31.8 (SD=8.5) to 27.2 (SD=6.2), p < .05), effect size of 0.59 • Children receiving G1 scored significantly higher on standard scores of adaptive behavior. • Significant improvements were found in maladaptive behaviors and excess and deficit behaviors as compared with G2 • Largest gains were observed during the first year. Effect size on all measures at year one were moderate to large
Flanagan et al. 2012[85-87, 89] Canada **G1:** Intensive behavioral intervention, 61/61 **G2:** Wait list control (matched by age), 61/61 Quality: Fair	**G1:** 42.93 ± 11.53 **G2:** 42.79 ± 10.51 NR	• In 2008 retrospective case series (Perry 2008) reporting on ~30% of G1 participants ASD severity (CARS), cognitive level, adaptive behavior, and rate of development improved significantly (all p <.001); outcomes varied across children: approximately 25% showed substantial improvements, 30% showed clinically significant improvement, 19% showed some/modest improvement, 25% showed no improvement or worsening of outcome. Analyses of a subset of the total participants (n=89) showed similar improvements (Freeman 2010) • Age (younger at baseline), IQ, adaptive behavior, and ASD severity were correlated with outcome; IQ was strongest predictor, accounting for 5-12% of the variance in outcomes (Perry 2011); in sub-set analysis (Shine 2010), duration of intervention also associated with better outcomes • ASD severity improved for G1 vs. G2 as did Vineland composite standard and ratio scores and IQ estimates (p values ≤ .033, effect sizes ranging from 0.53 to 0.83); 19 point difference in IQ at end of intervention in favor of G1 • Younger age at intervention and higher adaptive skills associated with better outcomes; adaptive skills also associated with better outcomes for G2. Duration of intervention became nonsignificant after intervention type was entered into statistical models (Flanagan 2012)

Table 6. Key outcomes of ABA-based early intervention studies, continued

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Months ± SD IQ, Mean ± SD	Key Outcomes
Itzchak et al. 2011[80, 81] Israel **G1:** ABA-based approach, 45/45 **G2:** Eclectic approach, 33/33 Quality: Fair	**G1:** 25.1 ± 3.9 **G2:** 26.0 ± 4.6 **G1:** 72.2 ± 19.2 **G2:** 73.3 ± 22.2	• Cognitive abilities (Mullen Scales) and overall Vineland raw scores improved in both groups (p<.001) over time; no significant differences between groups at followup; overall Vineland standard scores improved for both groups (p<.05) • Vineland motor skills domain decreased over time for both groups (p<.001); Children in G1+G2 with lower severity (ADOS) improved significantly more than those with higher severity on cognitive and adaptive measures; both groups declined on measures of motor skills, with greater decline for those with higher severity • G2 participants with lower severity improved significantly on Vineland communication and socialization measures compared with G1 (p<.001) • In analyses combining G1 and G2, higher cognitive abilities at baseline, particularly verbal abilities, and older maternal age were associated with greater adaptive skills at followup (p<.05); among those with greater severity, greater verbal ability was associated with better adaptive skills at followup (r=.672, p<.001) • Cognitive gains greater for those with lower severity (p<.01) and older, more educated mothers (p values <.001, .05); younger children had a better chance of cognitive improvement with intervention (p=NS)
Kovshoff et al. 2011[78, 79] UK **G1:** Early intensive intervention (publicly-funded or privately purchased), 23/23 **G2:** Usual care, 21/18 Quality: Poor	**G1:** 35.7 ± 4.0 **G2:** 38.4 ± 4.4 **G1:** 61.43 ± 16.43 **G2:** 62.33 ± 16.64	• Groups differed significantly on age at baseline (p<.05) • IQ, mental age, and language comprehension improved significantly for G1 vs. G2 after 24 months of intervention (p≤.05); effect size for IQ change=0.77 • Vineland daily living and motor skills scores improved for G1 vs. G2 (p<.05) but composite, communication, severity, and socialization scores did not differ significantly between groups at the 24 month followup • Parents noted more positive social behavior for G1 vs. G2 at the 24 month followup; responders had higher IQ, higher mental age, higher Vineland composite, communication, and socialization scores, lower motor skills, more behavior problems, and more autistic symptoms and fewer hours of intervention in Year 2 • At 2-year followup no significant group differences in IQ, adaptive behavior, communication, socialization, or behavior; more G1 participants achieved standard score on receptive language measure vs. G2 (p=.048) • In analyses of G1 participants in privately purchased vs. publicly funded early intensive intervention programs, IQ declined for publicly funded group compared with control or privately purchased participants (p<.0001); privately purchased participants maintained IQ and adaptive behavior gains from end of intervention to the 2 year followup. Publicly funded group had more severe ASD symptoms, lower adaptive behavior, and received less intensive intervention than the privately purchased group

ABA-applied behavior analysis; ADOS-Autism Diagnostic Observation Schedule; ASD-autism spectrum disorder; CARS-Childhood Autism Rating Scale; G-group; IQ-intelligence quotient; LEAP- Learning Experiences and Alternate Program for Preschoolers and their Parents; N-number; PDD-NOS-Pervasive Developmental Disorder-Not Otherwise Specified; SD=standard deviation; TEACCH- Treatment and Education of Autistic and Related Communication-Handicapped Children

Parent Training Approaches

One good quality RCT examining parent training[94] was conducted in Australia and compared two variations of the Building Blocks® program (Groups 1 and 2) to waitlisted controls. Mean child ages at enrollment ranged from 41.5 to 43.7 months. Mean IQs ranged from 57-66. Treatment duration was 40 weeks. Not all enrolled children had autism spectrum diagnoses; the breakdown was 87.5 percent of Group 1, 69 percent of Group 2, and 60.7 percent of the control group. To be enrolled in Group 2, children had to have a baseline level of "social maturity," a lack of "high levels" of problem behavior, and parents willing to attend sessions. Group 1 (n at follow-up=27) received individualized 2-hour visits every 2 weeks in the home environment. Group 2 (n=29) received weekly manualized, 2-hour, center-based sessions in small groups of 4 to 6 children, as well as parent training and a parent support group. The control group (n=28) comprised a non-randomized treatment comparison waitlist. All groups received concomitant additional interventions classified as educational (Group 1: 2.37 interventions ± 1.28; Group 2: 2.41 ± 1.50; control: 3.11 ± 1.64) or ASD-specific (Group 1: .22 ± .42; Group 2: .14 ± .35; control: .54 ± .79). Providers were multidisciplinary teams of teachers, speech-language pathologists, occupational therapists and psychologists.

Children in all three groups showed significant improvements in Vineland Communication scores. Compared with Group 1, children in Group 2 had significantly greater improvement in language comprehension and expression as measured by the Reynell Developmental Language Scales. Waitlisted children had significantly greater improvements in follow-up Vineland Socialization scores than children in either treatment group. No other significant differences emerged among the three groups on other child outcomes. When analyses were limited only to children with autism spectrum diagnoses, the magnitude of the effects increased but the presence of statistical significance did not change.[94]

Two prospective cohort studies also received good quality ratings. The first was conducted in Australia[98] and compared professional-led parent training (n=17; mean child age, 36.38 months ± 7.54; 88.2% male) to a self-directed video-based parent intervention (n=22; mean=35.71 months ± 6.92; 72.7% male). Nearly 80 percent (77%) of participants were diagnosed with autism and 23 percent with an ASD. Mean IQ was 53.06 ± 9.06 for the professionally led group and 52.86 ± 6.53 for the video-based group. Exclusion criteria included being enrolled in early intervention, passing the Modified Checklist for Autism in Toddlers (M-CHAT), or receiving more than 20 hours/week of services. No information was provided about manualization.

In the professionally led group, parents attended a two-day group workshop and completed a series of 10 hour-long home visits, which occurred two times a week for 5 to 6 weeks. These visits focused on parental stress and child communication. In the video group, parents received an interactive instructional DVD called "Being Responsive: You and Your Child with Autism." They independently completed video lessons and accompanying worksheets. Followup assessments were conducted 3 months after treatment finished. All outcomes were based on parent report. Children in the professionally led arm showed significantly greater improvement in social communication than children in the video-based arm, regardless of baseline scores. Parents in the professionally led group also reported reduced child-related stress relative to parents in the video group, with fathers reporting more stress than mothers in both groups. Parents in the professionally led group with low baseline self-efficacy reported higher followup self-efficacy levels than parents in the video arm.[98]

The second good quality prospective cohort study was conducted in Italy and reported in two papers.[99, 100] It compared staff- and parent-led ABA-based intervention (n=24, 92% male; mean

age=55.67 ± 17.63 months) to eclectic community-based therapy (n=20, 95% male; mean age=41.94 ± 13.07 months). Group assignments were not random and were based upon parental preference. Children were excluded based on the presence of major medical issues. In the parent training group, children alternated between one week (average of 25 hours) of therapist-led center-based intervention (discrete trial training, incidental teaching, natural environment teaching) and 3 weeks (average of 14 hours/week) of parent-led home intervention. Treatment focused on individual skills, problem behaviors, and facilitated play and social interactions. In the eclectic group, children received in-home developmental and cognitive behavioral treatments (approximately 12 hours/week) with minimal parent involvement. Treatment goals were based upon staff expertise and preferences.

Compared with the eclectic group, children in the parent training arm showed a significant decrease in autism symptom severity and increases in language production and mental development. The parents of children in the eclectic group reported that their children showed improved socialization and motor skills, but this was not confirmed by behavioral observation. In the parent training group, older children achieved better adaptive behavior outcomes; younger children made more gains in early language comprehension and production. Children who gained more language comprehension had higher adaptive behavior scores pre-treatment. Pre-treatment language comprehension predicted post-treatment language production. In the eclectic group, higher pre-treatment mental development state and early language skills predicted better outcome on parent-reported adaptive behaviors. Initial higher adaptive behaviors predicted better post-treatment early language comprehension. In both groups, child outcomes on early language skills, mental developmental state, and adaptive behaviors were significantly influenced by self-reported parental stress, children's ability to respond correctly to prompts, the number and difficulty of treatment targets, and children's problem behaviors in sessions. Children who were perceived by their parents as more difficult had less improvement in autism severity.[99, 100]

Two studies compared interventions focused on increasing parental responsivity. A good quality RCT from Europe[71, 103] compared treatment-as-usual + a manualized, communication-focused parent training (n=14, median age 48 months) to treatment-as-usual alone (n=14, median age=51 months) over 12 months. The intervention focused exclusively on parents and targeted increased parental response to child communication. The additional targeted treatment consisted of a recommended 30 minutes/day of parent-led intervention. Parents received monthly training for 6 months followed by training every 2 months for another 6 months. The intensity of treatment as usual alone was not reported but approaches consisted of speech pathology and ABA-based community treatments. The additional treatment group showed improvements in autism symptoms, expressive language, and number of communicative acts during interactions with parents. Parents in the additional treatment group showed increased responsiveness to their children during videotaped interactions, which was correlated with reduced autism symptom severity. No between-group differences were found in adaptive behavior or parenting stress. Greater language gains were seen in children who were younger with lower functioning levels at baseline.

A second fair quality RCT conducted in the United States also focused on enhancing parental responsivity and child communication.[91] It compared Hanen's More Than Words intervention to treatment-as-usual. The More Than Words group (n=29, mean age=21.11 ± 2.71 months) received eight manualized group sessions with parents only and three in-home individualized parent-child sessions over a span of 3.5 months, whereas the control group (n=26, mean age=21.61 ± 2.82 months) received no treatment or treatment as usual. There was no treatment

effect on parental responsivity. The More Than Words group showed differential effects on child communication depending on children's baseline object interest; children with lower levels of baseline object interest had greater growth in communication skills, whereas children with higher levels of object interest showed attenuated growth.

A good quality RCT out of the United States compared the manualized Assessment Evaluation and Programming System for Infants (AEPS) with and without additional joint attention and social interaction opportunities.[101, 102] Both the AEPS group (n=24, mean age=28.6 ± 2.6 months; mean intervention hours=205.66 ± 18.63) and the control (n=24; mean age=28.8 ± 2.8 months; mean intervention hours=196 ± 21) received identical amounts of classroom-based treatment (10 hours/week), home-based parent training (1.5 hours/month), parent education (38 hours), and intervention methods. However, AEPS children received extra training in "interpersonal synchrony," targeting the three outcome variables of socially engaged imitation, initiation of joint attention, and shared positive affect. No significant ($p < .05$) differences emerged post-treatment on variables of interest. At the 6-month followup, the AEPS treatment group engaged in significantly more socially engaged interaction than controls ($p < .05$), with most of the growth in this skill occurring during the treatment period ($p < .05$) but not during followup (p=.24). No between-group differences were found for initiations of joint attention, shared positive affect, expressive language, or nonverbal problem solving. The AEPS group showed significant growth over time for all variables (p values < .01), but the control group only showed significant growth for expressive language (p=.01). Combined group analyses including 34 children from both the AEPS and control groups examined long-term outcomes an average of 37.6 months after the end of treatment (mean participant age=72.6 ± months). In this sample, cognitive skills and Vineland-II communication standard scores increased significantly from baseline (mean change 21.4 ± 22.9, effect size=1.02, p<.001 and 12.7 ± 19.4, effect size=0.81, p<.001, respectively), but there was no significant change in autism symptom severity based on the ADOS.

A fair quality prospective study[93] compared outcomes for four different types of intervention after 9 months of treatment: 1:1 home-based, manualized ABA (n=14, mean age=39 ± 6.9 months); special education classroom enrollment (n=21, mean age=41.5 ± 4.0 months); comparatively low-intensity, home-based, manualized behavioral intervention ("portage;" n=18, mean age 39.5 ± 6.3 months), and 1:1 behavioral intervention ("local authority") that included an intensive introductory 5-day parent training component (n=13, mean age=40.2 ± 6.3 months). The home-based ABA group received an average of 30.4 hours/week of intervention, 28.3 of which were 1:1. The special education group received an average of 12.7 hours/week (3.1 hours 1:1). The portage group received an average of 8.5 hours/week (6.5 1:1), and the local authority group received an average of 12.6 hours/week (12.2 1:1). Participants were not receiving any other teaching interventions during the study.

Post-treatment, mean cognitive and adaptive scores were not significantly different across groups. Children in the home-based ABA group showed significant improvements in educational outcomes as measured by the British Abilities Scale relative to other groups (p<.05). The authors created composite scores based on cognitive, adaptive, and educational functioning, but between-group comparisons only approached significance (p<.06). Baseline autism severity and total intervention hours did modify effects of treatment significantly. First, baseline ASD severity was inversely related to composite change scores for all but the home-based ABA group and was positively related that group. That is, children with more severe autism symptoms made more progress in ABA and less in the other intervention groups. Second, more intervention time was

negatively related to composite change scores for children in ABA but not in the other groups. More hours of ABA were associated with less progress relative to school enrollment or other home-based interventions.[93]

One fair quality U.S. RCT compared parent-delivered ESDM to community-based treatment-as-usual.[96] The ESDM group included 49 children (mean age 21.02 ± 3.51 months, mean developmental quotient [DQ]=64.88 ± 17.22); their parents completed 12 1-hour sessions that included manualized parent-training and coaching. Both the ESDM group and the community group (N=49; mean age=20.94 ± 3.42 months, mean DQ=63.08 ± 15.93) continued receiving community-based treatment-as-usual services as well, including the Developmental, Individual Difference, Relationship-based (DIR) model, TEACCH, ABA, and occupational and speech therapies (range of hours: 0-15.9), with the community group receiving significantly more intervention hours at the second time point (mean 3.68 vs. 1.48; $p < .05$). Compared with the ESDM group, children in the community-based arm had more severe social affect deficits, poorer imitation skills, and higher nonsocial orienting scores at baseline ($p < .05$). After treatment, both groups showed improvement in DQ and ADOS Social Affect scores with no main effects of group assignment. Both groups of parents showed significant increases in parent-child interaction behaviors, with greater increases in the ESDM group (effect size=.57) than the community-based group (.37). When examining combined groups, two key effects emerged. First, total intervention hours were associated with reduced restrictive and repetitive behavior and nonsocial orienting and improved DQ and vocabulary comprehension. Second, children younger than 24 months showed greater increases in DQ scores (effect size=-1.20, p=.002).

A fair quality RCT from Asia examined DIR/Floortime (n=15) compared with center-based ABA (n=16).[90] Groups were stratified based on age (24-47 months, 28-72 months) and autism severity, based upon CARS scores. Both groups continued to receive treatment-as-usual, including enrollment in preschool programs and community-based services (such as speech or behavioral therapies.) Relative to the center-based group, the DIR/Floortime group showed significant improvement on the Functional Emotional Assessment Scale ($p < .05$) and autism symptoms as rated by the CARS (2.9 vs. .08, $p < .01$). Parents in the DIR/Floortime group also rated their children as showing significant improvements in emotional development ($p < .01$).

Two poor quality studies, a prospective cohort study from Europe[95] and a crossover RCT from China,[97] compared parent training to lower intensity supportive interventions. Mean ages ranged from 25.33-33.6 months. Both involved home visits and working with children and parents. The lower intensity treatment model, Autism-1-2-3, compared two groups that received the same series of 10 half-hour child- and parent-training sessions, with one group having a lagged start date and serving as a control. It did not yield group differences on autism symptoms, language skills, or parent stress scores.[97] The higher intensity model, Keyhole, incorporated elements of Hanen's More Than Words and the TEACCH programs. It compared 15 to 18 home visits over a 9 month period (n=35) targeting adaptive skills, autism symptoms, and parent stress to a lower-intensity intervention model (n=26; 5 home visits, no additional services or supports). Compared with the lower-intensity group, children in the Keyhole intervention showed improved adaptive, imitation, and communication skills, based upon parent report. Mothers in in the Keyhole group also reported improved health but not stress.[95]

Table 7. Key outcomes of early intervention studies with parent training components

Author, year, country Groups, N enrollment/N final Study quality	Age, mean months ± SD IQ, mean ± SD	Key outcomes
Roberts et al. 2011[94] Australia **G1**: Individualized home-based program, 34/27 **G2**: Small group center-based program combined with parent training and support group, 33/29 G3: Waitlist, 28/28 Quality: Good	**Age:** **G1**: 41.5 **G2**: 43.1 **G3:** 43.7 **IQ:** **G1**: 57 ± 11.7 **G2**: 66 ± 17.7 **G3:** 63.3 ± 15.5	• Significant greater improvement in Reynell comprehension standard score for G2 compared with G1 (-7.3; 95% CI (-13.9, - 0.7), p=0.02) • Greater improvement for expression standard score of the Reynell for the G2 compared with G1 (-3.0; 95% CI (-9.0, 2.9), P=0.31) • Reynell standard comprehension and expression scores G3 performed better than G1, but not significantly • For the Reynell standard comprehension and expression scores G2 performed better than G3 but not significantly. • G3 improved significantly more than the G1 for the social scale of the Vineland • No statistically significant differences among the three groups for other child outcomes. When analyses were limited only to children with autism spectrum diagnoses, the magnitude of the effects increased but the presence or absence of statistical significance did not. • Parent outcomes: Parenting: statistically significant differences favoring G2 vs. G1 • No significant difference between groups for stress
Strauss et al, 2012[99, 100] Italy **G1**: Staff & parent mediated early intervention, 24/24 **G2**: Eclectic, 20/20 Quality: Good	**G1**: 55.67 ± 17.63 **G2**: 41.94 ± 13.07 **G1**: 55.65 ± 20.06 **G2**: 74.29 ± 29.37	• Compared with G2, children in G1 showed significant decrease in autism symptom severity, increases in language production and mental development • Compared with G1, children in G2 had improved parent-reported socialization and motor skills • In G1, older children achieved better adaptive behavior outcomes; younger children made more gains in early language comprehension and production. Children who gained more language comprehension had higher adaptive behavior scores pre-treatment. Pre-treatment language comprehension predicted post-treatment language production • In G2, higher pre-treatment mental development state and early language skills predicted better outcome on adaptive behaviors. Initial higher adaptive behaviors predicted better post-treatment early language comprehension. • In both groups, child outcomes on early language skills, mental developmental state and adaptive behaviors were significantly influenced by parental stress, child ability to respond correctly to prompts, number and difficulty of treatment targets, and child problem behaviors in sessions. The predictive power of parental stress on outcome autism severity was modified by perception of difficult child, with higher perceptions of difficulty associated with lower decreases in autism severity • Less parent inclusion in treatment provision resulted in decreased perceptions of a difficult child and less parental stress

Table 7. Key outcomes of early intervention studies with parent training components, continued

Author, year, country Groups, N enrollment/N final Study quality	Age, mean months ± SD IQ, mean ± SD	Key outcomes
Keen et al. 2010[98] Australia **G1:** Professional parent intervention, 17 families/NR **G2:** Self-directed video based parent intervention, 22 families/NR Quality: Good	**G1:** 36.38 ± 7.54 **G2:** 35.71 ± 6.92 **G1:** 53.06 ± 9.06 **G2:** 52.86 ± 6.53	• G1 showed significantly greater improvement on social communication at followup than G2 regardless of values at baseline • Parents low in self-efficacy at baseline demonstrated relatively higher levels of self-efficacy if they received G1 vs. G2 • G1 reduced child-related stress relative to G2 for both mothers and fathers • Fathers reported higher levels of stress than mothers in both groups. • Behavior sample scores at followup not affected by group condition • All outcomes are based on parent report.
Oosterling et al. 2010[92] **G1:** Nonintensive parent training+specialized preschool, 40/36 **G2:** Specialized preschool, 35/31 Quality: Fair	**G1:** 35.2 ± 5.5 **G2:** 33.3 ± 6.4 **G1:** 58.4 ± 16.8 **G2:** 58.0 ± 16.9	• No between group differences on language development after 12 months of intervention, though language skills within groups improved over time • No differences in CGI-Improvement scores (G1: 57% much improved, G2: 52% much improved) • No significant effects on parenting skills in either group; engagement, early social communication precursors, parental skills not found to be mediators of effects. DQ not a significant moderator
Rogers et al. 2012[96] US **G1**: Parent-delivered Early Start Denver mode (ESDM)l, 49/49 **G2**: Community treatment as usual, 49/49 Quality: Fair	**G1:** 21.02 ± 3.51 **G2:** 20.94 ± 3.42 **G1:** 64.88 ± 17.22 **G2:** 63.08 ± 15.93	• At followup, G1 received mean 1.48 hrs treatment/week G2 received 3.68 ($p<.05$) • G2 had more severe social affect symptoms at baseline, poorer imitation and nonsocial orienting scores compared with G1 ($p<.05$) • No significant group differences on ADOS scores or measures of development at followup • Measures of parent acquisition of parent-child interaction skills did not differ between groups at followup • Social orienting and imitation skills were not found to be moderators of outcomes; increased hours of intervention and younger child age were significantly associated with improved developmental and vocabulary scores in a pooled analysis ($p\leq.05$). In analyses by group, age and hours of intervention associated with improvements in vocabulary for G1 ($p\leq.05$)

Table 7. Key outcomes of early intervention studies with parent training components, continued

Author, year, country Groups, N enrollment/N final Study quality	Age, mean months ± SD IQ, mean ± SD	Key outcomes
Dawson et al. 2012[72, 84] US **G1:** ESDM, 24/24 **G2:** Community-based interventions, 24/21 Quality: Good	**G1:** 23.9 ± 4.0 **G2:** 23.1 ± 3.9 **G1:** 61.0 ± 9.2 **G2:** 59.4 ± 8.6	1 year outcomes: • Significantly greater improvement in IQ for G1 (154 vs. 22 pts) compared with G2 • No adaptive behavior differences 2 year outcomes: • Significantly more improvement in G1 vs. G2 on IQ; receptive language, and expressive language • Adaptive behavior improvements in both groups (all domains except socialization); significantly greater improvements in G1; no change in ADOS severity scores or repetitive behavior • Diagnostic shift toward milder diagnosis (PDD-NOS) greater for ESDM group • No differences between groups in EEG measurements of perceptual face processing • EEG measures of engagement/cognitive processing comparable to those of typically developing children for G1 children with usable EEG data; 11/15 G1 participants and 4/14 G2 showed faster neural response to faces vs. objects
Reed et al. 2012[93] UK **G1:** ABA, 14 **G2:** Special nursery, 21 **G3:** Portage, 18 **G4:** Local authority-developed parent training, 13 Quality: Poor	**G1:** 39.0 ± 6.9 **G2:** 41.5 ± 4.0 **G3:** 39.5 ± 6.3 **G4:** 40.2 ± 6.3 **G1:** 55.1 ± 17.3 **G2:** 52.2 ± 17.1 **G3:** 54.0 ± 15.4 **G4:** 51.7 ± 14.5	• Scores on cognitive and adaptive measures were not significantly different among groups • Scores on British Abilities Scale improved for G1 vs. G2-G4 ($p < .05$) • Composite change scores (mean of change scores on cognitive, adaptive, and educational measures) were not statistically significantly different across groups, although G1 vs. G2-4 and G2 vs. G3-4 approached significance ($p < .06$) • Composite change scores were inversely related to initial ASD severity for G2-G4 but positively related for G1; the strength of that relationship only differed significantly between G1 and G3 ($p < .05$) • As time in intervention increased, composite scores improved for G2-G4 but worsened for G1 ($p < .05$). No differences were found in the amount of improvement between G2-4
Landa et al. 2012[101, 102] US **G1:** Assessment Evaluation and Programming System for Infants and Children (AEPS) curriculum+ additional joint attention and social interaction opportunities, 25/24 **G2:** AEPS curriculum, 25/24 Quality: Good	**G1:** 28.6 ± 2.6 **G2:** 28.8 ± 2.8 **G1+G2:** 60.1 ± 11.9	• Greater socially engaged imitation in G1 compared with G2 at end of intervention and at 6-month followup (effect size=0.86, p.01); growth occurred during intervention period vs. followup period • Initiations of joint attention did not differ significantly between groups at the 6-month followup, though each group improved over time • Measures of expressive language and nonverbal cognition did not differ between groups at the 6-month followup • At long-term followup of G1+G2 (n=34) at mean 37.6 months after end of intervention (mean age=72.6 ± 17.5 months), IQ and Vineland communication scores increased from baseline (mean change 21.4 ± 22.9, effect size=1.02, p<.001 and 12.7 ± 19.4, effect size=0.81, p<.001, respectively) • No change in symptom severity (ADOS) at the long-term followup

Table 7. Key outcomes of early intervention studies with parent training components, continued

Author, year, country Groups, N enrollment/N final Study quality	Age, mean months ± SD IQ, mean ± SD	Key outcomes
Pajareya et al. 2011[90] Thailand **G1:** DIR/Floortime,16/15 **G2:** Usual care, 16/16 Quality: Fair	**G1:** 56.6 ± 10.1 **G2:** 51.5 ± 13.9 NR	• G1 improved significantly on the Functional Emotional Assessment Scale compared with G2 (p=.045) • CARS scores decreased (improved) for G1 vs. G2 (mean change 2.9 vs. 0.8, p=.004) • G1 scores on parent-rated measure of emotional development significantly improved compared with G2 (mean change 7.7 vs. 0.8, p=.007)
Carter et al. 2011[91] US **G1**: More than Words, 32/29 **G2**: Control, 30/26 Quality: Fair	**G1:** 21.11 ± 2.71 **G2**: 21.51 ± 2.82 NR	• No treatment effect on parental responsivity • G1 showed differential effects on child communication depending on a baseline child factor • Children with lower levels of baseline object interest exhibited facilitated growth in communication • Children with higher levels of object interest exhibited growth attenuation
Aldred et al. 2011[71, 103] UK **G1:** Parent training in social communication intervention plus community intervention, 14/14 **G2:** Community intervention, 14/14 Quality: Good	**G1:** 51.4 ± 11.8 **G2:** 50.9 ± 16.3 NR	• 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. • Increased parental synchrony (communication which maintained vs. redirected or controlled child responses) in G1 associated with reduction in child ADOS score (decreased impairment, p=.014); reduction in synchrony for G2 and small increase in mean ADOS scores. In tests of mediation, change in parental synchrony accounted for 34% of total treatment effect on ADOS outcome
McConkey et al., 2010[95] UK **G1**: Keyhole early intervention program, 36/35 **G2**: Control, 26/26 Quality: Poor	**G1**: 2.8 years **G2**: 3.4 years NR	• G1 showed significant improvements on different indices of communication than G2 • Mothers improved on measures of health G1 more than G2 but not of stress • Higher percentage of parents in G2 reported the children were improving on language and imitation at Time 1 compared with G1 percentages comparable at Time 2 • Only parents in G1 reported significant improvements from Time 1 to Time 2 on language, imitation and relating to others
Wong et al., 2010[97] China **G1**: Early intervention, 9/9 **G2**: Control, 8/8 Quality: Poor	**G1**: 25.33 ± 6 **G2**: 27.88 ± 5.57 **G1**: 17.85 ± 4.16 **G2**: 17.91 ± 4.49	• No significant group difference on communication, reciprocal social interaction or symbolic play • No between group differences on parent observation on language and relationship to people • No group difference on total parent stress scores

ADOS-Autism Diagnostic Interview Schedule; CI-confidence interval; CGI-Clinical Global Impression; DQ-developmental quotient; EEG-electroencephalography; ESDM-Early Start Denver Model; G-group; IQ-intelligence quotient; N=number; NR-not reported; PDD-NOS-Pervasive Developmental Disorder-Not Otherwise Specified; SD-standard deviation

Social Skills Interventions

Key Points

- Ten behavioral studies examined different social skill interventions and included children and adolescents with ASD. Overall, the quality of the studies improved in comparison to the 2011 review. Two studies were rated as good quality, while eight studies were fair quality.
- Most studies included school-aged children, without concomitant intellectual disability or language deficits. Most children were high functioning (IQ>70).
- Most studies reported short-term gains in social skills and emotion recognition as reported by parents or within study measures. Maintenance and generalization of skills beyond the treatment context was addressed within the majority of the studies, but with variable results.
- The diversity of the intervention protocols and assessments utilized to measure outcomes continues to be a limiting factor for determining effectiveness of social skills interventions.

Overview of the Literature

In addition to the nine comparative studies assessing social skills included in the 2011 review, eight RCTs of fair[107-109] and poor[110-114] quality and one poor quality retrospective cohort[115]), 10 studies of good[116, 117] and fair[118-125] quality addressed interventions targeting social skills. Studies addressed in the current review included a total of roughly 375 participants (mean/study=37). Six RCTs were conducted in the United States,[117-120, 122, 126] one in Europe,[127] and 2 in Australia.[116, 125] One nonrandomized study was also conducted in Australia.[124] Participant ages across studies ranged from 4 to 13 years, and participants typically had high functioning ASD (IQ>70). Studies assessed group-based approaches including replications of studies evaluating the Skillstreaming model;[119, 120, 122, 126] incorporated peer-mediated components;[117, 118, 128] and targeted emotion recognition in children with ASD.[116, 121, 125]

Detailed Analysis

Four fair quality RCTs conducted in the US addressed group-based social skills approaches.[119, 120, 122, 126] Among these, three studies evaluated the manualized Skillstreaming model (Table 8).[120, 122, 126] The studies included between 13 and 52 total participants, all of whom were considered to be high functioning, and most of whom were male. One RCT compared a manualized performance-based approach, Sociodramatic Affective Relational Intervention, versus the knowledge-based Skillstreaming social skills intervention, which emphasizes social skills, face-emotion recognition, interest expansion, and interpretation of non-literal language. The study included 13 boys with ASD between the ages of 9 and 12. Weekly 90-minute sessions treatment sessions were held over 4 weeks after school. Treatment sessions, regardless of the intervention, included content covering considering others, emotions, consolidating, and generalization of skills. Participants in both groups increased in reciprocal friendship nominations and staff-reported social skills. Participants in the sociodramatic group interacted more with each and rated one another more favorably after one session, which slightly decreased over time. Skillstreaming participants also demonstrated gains in interactions and more favorable ratings over the course of the intervention, but at a slower rate as compared with the sociodramatic group. No significant differences in parent report of social functioning were demonstrated for either group.[122]

A second RCT[120] examined the short-term outcome of a 5-week trial of the Skillstreaming approach and replicates the intervention reported in a study[108] described in our 2011 review. The

study included 36 children (mean age=9.47), primarily male (94% of the total sample) with high functioning ASD (mean IQ=103) randomized either to Skillstreaming or a wait-list control group. Participants in the treatment group showed significant improvements in most parent-rated measures of social skills compared with the control group (Social Responsiveness Scale: effect size=0.625, p=.003; Adapted Skillstreaming Checklist: effect size=0.584, p=.006; Behavioral Assessment System for Children (BASC)-Withdrawal scale: effect size=1.055, p<.001); however, group differences on the BASC-Social Skills scale were not significant. Staff-report measures found similar outcomes, with significant improvements in autism disorder symptomology and program-targeted social skills, as well as a decrease in withdrawn behaviors in the treatment group compared with the control arm (effect sizes ranging from 0.69 to 1.4, p values ≤.007). Child-rated measures similarly improved in the Skillsteaming group compared with control (Skillstreaming Knowledge Assessment: effect size=1.272, p<.001; understanding of idioms: effect size=0.390, p<.001).[120]

Another RCT replicating the Skillstreaming model reported by Lopata et al.[120] included 35 children with high functioning ASD between the ages of 7 and 12.[126] Skillstreaming involved five 70-minute sessions treatment sessions per weekday over 5 weeks. Treatment sessions involved skill instruction (nonliteral language and face-emotion recognition) and practice as well as a behavioral system to encourage participation and decrease problem behaviors. Weekly 90-minute parent trainings were also conducted, which involved education on ASD as well as training on the treatment program. Scores on the parent-rated Skillstreaming Checklist, Social Responsiveness Scale, and Behavior Assessment System for Children-2 Withdrawal scales improved for the Skillstreaming group compared with the control (effect sizes 0.85, 0.67, 0.70 respectively, all p<.01). Child-rated measures also improved for the treatment group compared with control (Skillstreaming Knowledge Assessment effect size 1.15; language assessment=0.34, p<.001). No group differences were found in face-emotion recognition. Maintenance of effects on the Skillstreaming Knowledge Assessment and BASC Social Skills scale for the treatment group was demonstrated 2 to 3 months post-treatment (effect sizes 0.47 to 0.68).[126]

A final RCT examined the short-term outcome of a trial of a manualized outpatient 15-week social skills program, the Social Skills Group Intervention – High Functioning Autism (SS GRIN-HFA).[119] The study included 55 children, primarily male (98% of the total sample) with IQ > 85 randomized either to SS GRIN-HFA group (mean age 10.2 years) or to a traditional SS GRIN group (mean age 9.9). Participants in the SS GRIN-HFA group showed significant improvement in social skills, with significantly better scores than the control arm on all Social Responsiveness Scale domains except social cognition (effects sizes ranging from -0.67 to -0.94). In addition, parents of children in the treatment group reported significant improvement in the areas of their child's social awareness, motivation for social interaction, social communication skills, and unusual mannerisms associated with ASD. No significant difference was found between the treatment group and control group regarding child self-report of self-efficacy or loneliness.

Two RCTs[117, 118] and one nonrandomized controlled trial[128] assessed interventions targeting social skills and incorporating typically developing peers or siblings. Studies included 21 to 60 participants, generally with high functioning ASD. One RCT examined short-term outcomes of a trial of an outpatient peer tutor social skills training program.[117] The study included 44 children (mean age=9 years, IQ>70) who met criteria for a Pervasive Developmental Delay. Sixteen out of 23 participants in the treatment group were considered treatment responders as rated by their parents, compared with 0/18 in the control arm (p<=.001). Children with Asperger syndrome

were more likely to be responders compared with children with PDD-NOS (p=.03); IQ was not associated with response status. No significant differences were found between the treatment group and wait list group on social competence measures.

A second fair quality RCT evaluated child-directed social skills training (CHILD) compared with peer-mediated social skills training (PEER) applied to children with high-functioning autism attending regular education classrooms.[118] The study included 60 children (mean age = 8.14, mean IQ = 90.7) randomized to one of four treatment groups (n=15/group): 1) CHILD group 2) PEER group 3) CHILD+PEER and 4) a control group. Treatment occurred over 6 weeks. In the CHILD condition, it included 1:1 training and practice in social skills targeting deficits identified for each child. In the PEER arm, it included peer interaction focused on positive social modeling. Participants who received PEER interventions (PEER alone or PEER+CHILD) showed significant improvements in social network salience (prominence of a child within the classroom social network) compared with the other groups ($p \leq .006$). At the final followup 12 weeks after the end of the intervention, salience remained higher for the CHILD+PEER arm compared with CHILD alone and the control group but not compared with PEER alone. Teacher ratings of social skills also improved from baseline to final followup for the peer-mediated group as did measures of solitary engagement and joint attention.

One fair quality, non-randomized trial examined the effectiveness of including siblings in social skills training groups for boys with Asperger's Syndrome.[124] The study included 21 children with Asperger syndrome between the ages of 8 and 12. Investigators partially randomized participants to one of three treatment groups (first 15 randomly assigned to one of three groups; later recruits assigned based on whether they had an older sibling; if no sibling, participants were randomly assigned to "no sibling" training or wait-list control group). Eight weekly 2-hour sessions treatment sessions were held in a clinical setting. Treatment sessions included content covering nonverbal social cues, such as eye contact, body language, tone of voice, and facial expression. Techniques included extended time, repeated practice, conceptual explanations, role play, and use of social dilemmas. Participants were also assigned a different partner each week to encourage social interaction and cooperation. Sibling participants were not given any specific training or instruction other than what was provided as part of the treatment sessions. Homework tasks were given to facilitate generalization. Participants in the active treatment groups demonstrated significant improvement in identification of nonverbal cues to identify emotions compared with the waitlist control group. While the ability to identify social cues was maintained by the participants in the active treatment groups, no increase in skills was demonstrated at 3-months post-intervention. Parents in all groups rated socials skills for both children with ASD and siblings as improved over time. No difference in teacher report of social skills for target participants or siblings was demonstrated.

Three RCTs, one of good and two of fair quality, addressed interventions targeting emotion recognition in children with ASD.[116, 121, 125] Two studies used specialized DVDs to demonstrate emotions and one used a manualized, group-based intervention focused on Theory of Mind training, which includes recognizing emotions, understanding differences between fantasy and reality, perspective taking, and reasoning about other people's mental states. Two RCTs conducted in Australia (one good quality[116] and one fair[125]) assessed the outcome of The Transporters DVD series as an intervention for emotion recognition. The first RCT examined changes in emotion recognition and generalization of newly acquired skills to improvements in social perception skills over a 3-month period. The study included 55 children with autism between the ages of 4 and 7 randomly assigned to view either the Transporters DVD series or the

control DVD series (Thomas the Tank Engine) for four weeks (15 minutes per day in their home setting). Parents were also provided with a diary to record the number of hours watched per day. Compared with control participants, participants in the treatment group improved in emotion identification and matching of emotions (anger only) immediately following the intervention, with improvements maintained 3-months post-intervention. Gains were also seen in the treatment group 3-months post-intervention for identification of happiness and emotion recognition within situations. In both groups, no difference was found in affect recognition, theory of mind, or social skills immediately following the intervention or at the maintenance phase. Long term improvements in identification of happiness expressions were associated with greater ADOS severity, as was matching of emotions overall and of sadness specifically. Age was correlated with identification of fear expressions, affect recognition, and the mind reading desire-based task. Verbal IQ was also associated with some short term improvements.[116]

A second, 3-week RCT comparing The Transporters DVD with the control series included 25 children with PDD between the ages of 4 and 8. Parents were also provided with a user guide to facilitate their child's participation in watching the episodes as well as logbook to record the number of sessions watched per day. Participants in the treatment group improved on standardized measures of emotion and facial recognition, while both groups improved on social peer interest and eye contact. In both groups, no difference was found in gaze aversion or stereotyped behavior. This study provided little information on the demographics of the participants. This study also did not provide information on the user guide, which may be a confounding variable to the obtained findings. The authors also refer to Nonverbal IQ in one of their tables, but only administered the Block Design subtest, which does not measure nonverbal IQ.[125]

A final, fair-quality study examined the short-term outcome of a trial of a manualized Theory of Mind training program.[121] The study included 40 children (mean age=10 years) with a diagnosis of high functioning ASD and cognitive abilities within the normal range (mean IQ=100.1 in the treatment group and 103.3 in the control group). The participants were randomized either to a 16-week Theory of Mind training group or a wait list control group. Participants in the treatment group improved on their conceptual theory of mind skills compared with the control group (awareness of multiple emotions, effect size=0.84, $p<.05$; complex emotions, effect size=1.19, $p<.01$), but no significant differences were found between groups on elementary theory of mind understanding, self-reported emphatic skills, or parent-reported social behavior.

Table 8. Summary of outcomes of social skills studies

	Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
Group-based Social Skills Approaches	Lerner et al. 2012[122] US **G1:** Sociodramatic Affective Relational Intervention (SDARI), 7/7 **G2:** Skillstreaming, 6/6 Quality: Fair	**G1:** 10.86 ± 1.68 **G2:** 11.33 ± 1.63 NR	• Study included only boys with high functioning ASD, 69% diagnosed with Asperger syndrome • Compared with G2, G1 participants decreased in both positive and negative interactions over time (effect size=-1.17) • G2 participants increased in social preference (effect size=0.37); both groups increased in number of reciprocated friendship nominations (effect size=0.31, p=.048) and in interventionist-rated social skills (effect size=0.59, p=.002) • No significant effects on parent-rated measures
	Thomeer et al. 2012[126] US **G1:** Skillstreaming, 17/17 **G2:** Wait list control, 18/18 Quality: Fair	**G1:** 9.24 ± 1.64 **G2:** 9.39 ± 1.91 **G1:** 104.26 ± 14.13 **G2:** 103.42 ± 13.26	• Study replicates Lopata 2010[120] and included children with high functioning ASD (71% Asperger syndrome, mean IQ G1+G2=103.83 ± 13.49) • G1 scores on parent-rated Skillstreaming Checklist, Social Responsiveness Scale, and Behavior Assessment System for Children-2 Withdrawal scales improved compared with G2 (effect sizes 0.85, 0.67, 0.70 respectively, all p<.01) • G1 scores on child-rated Skillstreaming Knowledge Assessment and language measure improved compared with G2 (effect sizes 1.15, 0.34 respectively, p<.001) • G1 improved from baseline to followup 2-3 months post-intervention on the Skillstreaming Checklist (effect size=0.47, p=.006) and Behavior Assessment System for Children Social Skills scale (effect size=0.68, p=.004)
	Lopata et al. 2010[120] US **G1:** Skillstreaming, 18/18 **G2:** Wait list control, 18/18 Quality: Fair	**G1:** 9.39 ± 1.72 **G2:** 9.56 ± 1.54 **G1:** 101.63 ± 13.75 **G2:** 104.45 ± 15.46	• Study replicates intervention reported in earlier studies (Lopata 2006, 2008[108]) and included children with high functioning ASD, 78% with Asperger syndrome, 94% male • Most scores on parent-rated measures were improved for G1 vs. G2 (Social Responsiveness Scale effect size=0.625, p=.003; Adapted Skillstreaming Checklist effect size=0.584, p=.006; Behavioral Assessment System for Children (BASC)-Withdrawal effect size=1.055, p<.001). Differences on the BASC-Social Skills measure were not significant • Staff-rated measures were significantly improved for G1 vs. G2 (Social Responsiveness Scale effect size=0.711; BASC Withdrawal and Social Skills effect sizes ranging from 0.69 to 0.78, p≤.007; Adapted Skillstreaming Checklist effect size=1.421, p<.001 • Most child measures improved significantly for G1 vs. G2 (Skillstreaming Knowledge Assessment effect size=1.272, p<.001; understanding of idioms effect size=0.390, p<.001). Child Faces scores were not significantly different.

Table 8. Summary of outcomes of social skills studies, continued

	Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
Group-based Social Skills Approaches	DeRosier et al. 2010[119] US **G1:** Social Skills Group Intervention-High Functioning Autism (S.S.GRIN-HFA), 27/24 **G2:** Traditional S.S.GRIN, 28/28 Quality: Fair	**G1:** 10.2 ± 1.3 **G2:** 9.9 ± 1.1 NR	• Study included participants with high functioning ASD, 98% male • G1 improved significantly compared with G2 on all Social Responsiveness Scale domains except cognition (p≤.05, effect sizes ranged from -0.67 to -0.94) and on the Achieved Learning Questionnaire (effect size=0.75, p<.05) • Child reported measures of self-efficacy and loneliness did not differ by group
Peer Approaches	Koenig et al. 2010[117] US **G1:** Peer tutor social skills training, 25/23 **G2:** Wait list control, 19/18 Quality: Good	**G1:** 9.2 ± 1.2 **G2:** 9.3 ± 1.2 **G1:** 96.4 ± 20.5 **G2:** 95.9 ± 17.3	• Study included high functioning children with ASD (IQ≥70) • 16/23 G1 participants and 0/18 G2 were considered treatment responders (much improved or very much improved on CGI-I), p=.001 • Children with Asperger syndrome more likely to be responders vs. children with PDD-NOS, p=.03; no differences between those with autism and Asperger syndrome or PDD-NOS • IQ not associated with response status • No significant differences at followup within groups or between groups on social competence measures
	Kasari et al. 2012[118] US **G1:** Individualized child-directed social skills training (CHILD), 15/14 **G2:** Peer-mediated social skills training (PEER), 15/15 **G3:** CHILD+PEER, 15/15 **G4:** Control, 15/15 Quality: Fair	**G1:** 8.23 ± 1.48 **G2:** 7.60 ± 1.35 **G3:** 8.67 ± 1.68 **G4:** 8.07 ± 1.69 **G1:** 93.93 ± 19.60 **G2:** 84.80 ± 10.12 **G3:** 90.33 ± 14.17 **G4:** 95.07 ± 19.44	• Study included high functioning children with ASD attending regular education classrooms for ≥80% of day, overall mean IQ=90.97 ± 16.33; significantly more females in G2 compared with other groups, p=.004 • Social network salience increased for G2 and G3 compared with other groups, effect sizes for G2 ranged from 1.12 to 1.18 vs. G1 and G4 (p≤.006) at end of intervention; at followup 12 weeks post-intervention, salience significantly higher for G3 compared with G1 and G4 but not G2 • Solitary engagement on playground and joint attention improved at final followup for G2 • Teacher ratings of social skills improved from baseline for G2 (p=.01) but not G1, G3, or G4. No significant differences for any group at final followup

Table 8. Summary of outcomes of social skills studies, continued

	Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
Peer Approaches	Castorina et al. 2011[124] Australia **G1:** Social skills training with sibling, 7/7 **G2:** Social skills training without sibling, 8/8 **G3:** Wait list control, 6/6 Quality: Fair	**G1+G2+G3:** 10.30 ± 1.15 NR	• Study included only boys with Asperger syndrome • In post-hoc comparisons, both G1and G2 had significantly higher Child and Adolescent Social Perception measure scores than G3 at followup (p≤.003); differences between G1 and G2 were not significant • Ability to read social cues improved in G1 and G2 from baseline to end of intervention • No significant difference between groups on parent or teacher rated social skills measures (Social Skills Rating System)
Emotion Recognition Approaches	Williams et al. 2012[116] Australia **G1:** Emotion recognition training (Transporters DVD), 29/21 **G2:** Control (Thomas the Tank Engine DVD), 31/25 Quality: Good	**G1:** 62.83 months ± 11.17 **G2:** 61.93 months ± 9.91 **G1:** 77.93 ± 13.96 **G2:** 74.56 ± 13.58	• G1 improved in identification of expressions of anger (p=.01), overall emotion identification (p=.00) and identification of anger (p=.03) compared with G2 from baseline to end of intervention; Vineland socialization, theory of mind task scores, and affect recognition scores did not differ significantly between groups • Compared with G2, G1 improved on identification of happy facial expressions (p=.02) and mindreading situational task scores 3-months post-intervention; scores on identifying expressions of anger and on the theory of mind contextual task decreased for G1 vs. G2 (p≤ .02) • Long term improvements in identification of happiness expressions associated with greater ADOS severity. Age was correlated with identification of fear expressions, affect recognition. Verbal IQ was associated with some short term improvements
	Young et al. 2011[125] Australia **G1:** Emotion recognition training (Transporters DVD), 13/13 **G2:** Control (Thomas the Tank Engine DVD), 12/12 Quality: Fair	**G1+G2 (range):** 4-8 years **G1:** 11.31 (4.17) **G2:** 8.67 (4.05)	• Videos provided to groups differed in level of emphasis on emotion recognition • Affect recognition improved significantly in G1 vs. G2 (effect size=0.53, p<.001) as did Faces task scores (effect size=0.31, p=.005) • Both groups improved significantly on measures of social peer interest and eye contact; between group differences were not significant • Improvements in G1 were associated with extent of attention to faces in the DVD in G1 (r=0.59, p=.036) but not in G2; IQ was not correlated with improvements in either group

Table 8. Summary of outcomes of social skills studies, continued

	Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
Emotion Recognition Approaches	Begeer et al. 2010[121] Amsterdam **G1:** Theory of Mind training, 20/19 **G2:** Wait list control, 20/17 Quality: Fair	**G1:** 10.3 ± 1.3 **G2:** 10.3 ± 1.1 **G1:** 100.1 (15.3) **G2:** 103.3 (12.9)	• Study included children with high functioning ASD: 28% diagnosed with Asperger syndrome,67% with PDD-NOS • G1 improved on overall Theory of Mind test vs. G2 (effect size=0.75, p<.03) and on elementary theory of mind tasks (effect size=1.00, p<.01) but not on theory of mind precursors (e.g., perception, emotion recognition) • Significant improvements for G1 vs. G2 on some emotional awareness measures (multiple emotions, effect size=0.84, p<.05); complex emotions, effect size=1.19, p<.01) • No effects on self-reported empathy or parent-reported social skills

ADOS-Autism Diagnostic Observation Schedule; ASD-autism spectrum disorder; G-group; N=number; PDD-NOS-Pervasive Developmental Disorder-Not Otherwise Specified; SD-standard deviation

Play/Interaction-Based Interventions

Key Points

- Nine studies addressed interaction-based approaches: three good and five fair quality RCTs and one poor quality prospective cohort.
- Studies of interventions targeting joint attention and delivered by teachers, parents, and interventionists reported gains in joint attention skills in treatment groups compared with controls typically over a short duration (8 to 12 weeks). Children in both treatment and comparison groups typically received early intervention in addition to the targeted intervention.
- One small, poor quality study of an intervention targeting pretend play showed an increase in play dialog in both groups, with a greater increase in the intervention group.
- Studies targeting parental responsiveness to child communication reported increases in responsive parent behaviors in the treatment arms and limited increases in child communication.

Overview of the Literature

In addition to seven (reported in nine publications) comparative studies (two RCTs of fair[129-131] and five of poor[132-137] quality) addressing play- or interaction-based approaches described fully in the 2011 review, we identified nine studies (reported in13 papers) evaluating such interventions for the current review (Table 9). Among these nine studies, one includes a population addressed in the 2011 review.[130, 131, 138, 139] We considered three studies in the current review to be of good quality,[140-143] five of fair quality,[130, 131, 138, 139, 144-147] and one of poor quality.[148] Studies were conducted in the United States[130, 131, 138-144, 146-148] and Europe[145] and included a total of 291 participants between the ages of 21 and 82 months. Intervention duration ranged from 6 to 12 weeks; three studies reported long term (≥12 months post-intervention) followup of participants.[130, 131, 138-140, 146] While all studies used approaches incorporating focused interactions directed by teachers or interventionists[130, 131, 138, 139, 141-143, 145, 147, 148] or

parents/caregivers,[140, 144, 149] studies typically addressed outcomes related to joint attention, pretend play, imitation, or child/parent communication.

Detailed Analysis

Studies Addressing Joint Attention Outcomes

A fair quality pilot RCT evaluating a teacher-implemented joint attention intervention randomized child-teacher dyads in public preschools to either intervention (n=9 children, mean child age=46 ±5 months, mean mental age=30.3 ±5.01 months) or wait list control (n=7, mean age=43.01±6 months, mean mental age=33.8±8.74 months).[147] The manualized JASP/ER (Joint Attention and Symbolic Play/Engagement and Regulation) intervention trained teachers in eleven key strategies including setting up the environment, following the child's lead, imitating the child's play action, contingent language, and modeling joint attention. Teachers received a 1-hour training workshop and 1-hour of individual training with the child from a JASP/ER interventionist per week. Interventionists also instructed teachers to use JASP/ER strategies daily. At the 5-week followup, children in the intervention group improved in total initiations of joint attention and in pointing compared with the control arm ($p<.005$) and in showing ($p<.01$) in classroom observations (large effect sizes for each measure, 1.85 to 2.02). Groups did not differ on measures of looking or giving. Most scores on the Early Social Communication Scales joint attention measures and frequency of joint attention initiations in videotaped interactions did not differ significantly between groups. Object engagement declined and supported engagement improved in the treatment group compared with control (large effect sizes, $d=1.24$ to 1.41, $p\leq.05$). Observations of teachers also demonstrated increased use of JASP/ER strategies in the treatment arm.

In another good quality pilot RCT of JASP/ER, investigators randomized minimally verbal (<10 spontaneous functional communicative words) preschoolers enrolled in intensive ABA-based interventions for at least 12 months to either JASP/ER or control (standard intensive preschool, n=8, mean age=54.68±10.25, mean mental age=13.91±3.85).[141] Treatment group participants (n=7, mean age=48.73 ± 11.68 months, mean mental age=17.21 ± 3.91 months) received 1-hour of JASP/ER training per week in addition to the intensive preschool . At the 3-month followup, the JASP/ER group increased in play types and decreased time unengaged significantly from baseline ($p=.04$) while changes were not significant for the control group. The JASP/ER group also spent less time unengaged during class observations compared with the control group (effect size=1.63, $p=.05$), initiated more requesting gestures (effect size=1.51, $p=.01$) and evidenced more diversity of spontaneous play (effect size=0.81, $p=.04$). Groups did not differ on Early Social Communication Scales variables related to joint attention.

Another fair quality RCT[145] conducted in 59 Norwegian preschools over 8 weeks evaluated a manualized adaptation of a joint attention intervention reported below.[130, 131, 138, 139] Children in the intervention group (n=34, mean age=47.6 ± 8.30 months, DQ=53.3 ± 19.2) attended regular or specialized ASD preschools and also received up to 80 sessions (20 minutes twice daily, 5 days/week) of intervention focused on promoting joint attention and engagement within play activities. Children in the control group (n=27, age=50.3 ± 8.3 months, DQ=59.9 ± 19.7) also attended regular or specialized preschools. Groups did not differ in number of preschool hours or 1:1 training or support. The control group had greater expressive language age at baseline compared with the treatment group (mean 24.9 ± 12.8 vs. 18.8 ± 10.5, $p=.047$). At the 8-week followup, frequency of joint attention skills during teacher-child play were significantly better in

the treatment group compared with control (effect size=0.44) but the duration of joint engagement did not differ between groups. Duration of joint engagement was greater in mother-child play in the treatment group vs. control (mean 12.2% longer duration of joint engagement, effect size=0.67). While initiation of joint attention skills increased in the treatment group, group differences were not significant, thus effects on joint attention seen with teachers did not generalize. Frequency of joint attention initiation as measured on the Early Social Communication Scales did not differ between groups. Adjusting analyses to account for expressive language differences did not change results. Further, investigators found no putative moderators (age, DQ, language age, program philosophy) to be significant, suggesting that the intervention may be applicable across developmental levels.[145]

Another fair quality RCT comparing joint attention and symbolic play interventions delivered via an interventionist included 58 children with autism between 3 and 4 years of age. Investigators assessed language development, joint attention and play skills, and mother-child interactions at pre- and post-intervention and 6 and 12 months after the end of the 5 to 6 week intervention.[130, 131, 138, 139] Children in both groups showed significantly greater growth in expressive language, initiation of joint attention, and duration of child-initiated joint attention over time than did participants in the control group ($p<.01$ to $<.05$, moderate to large effect sizes). Growth in receptive language was not significantly affected by the intervention from pre-intervention to 12 months post-intervention. Children in the symbolic play group also showed significantly more growth in play level than did children in either the joint attention ($p<.01$) or control ($p<.001$) groups.

In a subsequent report on 52 of the 58 RCT participants assessing joint attention quality, both the joint attention and symbolic play groups improved in shared positive affect during joint attention and in shared positive affect with utterances during joint attention at 6 and 12 months post-intervention ($p<.05$) but not at intervention exit.[139] Differences between groups at the 6 and 12 month time points were not significant. The control group generally declined in instances of shared affect over the followup time points. Forty of the 58 participants in the RCT also participated in followup 5 years post-intervention.[138] Fifteen of 20 children in the joint attention group, 14 of 21 in the symbolic play group, and 11 of 17 in the control returned at 5 years; mean age across groups was 8 years and 8 months. Of the 40 participants, five were enrolled in regular education, 17 in regular education with some special education support, and 18 were in special education classrooms; placement did not differ among groups. At followup, 5/15 participants in the joint attention group, 1/14 in the symbolic play group, and 2/11 in the control arm were considered non-spectrum. Thirty-two of the 40 participants achieved valid scores on language assessments at followup. Ability to use spoken language at followup ("passing" the language assessments) was predicted by children's average play level at baseline ($p<.01$). Number of functional play types at baseline predicted greater cognitive skills. Age at baseline, initiation of joint attention, play level and treatment group assignment predicted subsequent vocabulary ability (all $p<.03$); these factors together explained 64 percent of spoken language variability.

In a fair quality RCT of a joint attention intervention adapted from this study[130, 131, 138, 139]investigators randomized 38 caregiver/child dyads to either immediate, parent-mediated treatment (n=19) or a wait list control group (n=19).[140] The 8-week treatment included individualized, developmentally appropriate play routines to promote parents' following of their children's interests and activities. Children in both groups ranged in age from 21 to 36 months (mean=30.82 months, mean mental age=19.2 months). At the end of intervention, children in the treatment group demonstrated less object-focused play, more responsiveness to joint attention,

more functional play acts, and more joint engagement than children in the control group ($p<.05$). Groups did not differ in initiations of joint attention, diversity of symbolic play, or unengaged actions. At followup of the treatment group 12 months after the end of intervention, results suggested maintenance of gains in joint engagement, response to joint attention, and reduction of object engagement, but changes in scores were not significant. Types of functional play acts improved at the 12-month followup ($p<.01$). In analyses of potential predictors of outcome, greater caregiver quality of involvement (rated by investigators) predicted increased joint engagement ($p<.05$) but not other play skills or engagement outcomes. Parent-rated adherence or competence did not predict changes in any outcome. Number of hours of other intervention similarly did not predict any outcomes.

Studies Addressing Pretend Play

One poor quality nonrandomized, crossover study conducted in a private preschool included 12 high functioning children with ASD (age range 55-75 months).[148] Intervention group participants received the Picture Me Playing intervention, which included scripted stories built around specific toys to model and encourage pretend play. Instances of play dialogue increased significantly following intervention for the treatment group compared with control (3.6 times more utterances over baseline vs. 1.79 times, $p<.05$), though frequency of play utterances in both groups improved from baseline. Gains in pretend play for both groups also generalized to a toy not used in the intervention and without scripted utterances.

Studies Addressing Imitation

A good quality pilot RCT of Reciprocal Imitation Training, which uses naturalistic approaches to promote imitation and social interaction, allocated 27 children to either Reciprocal Imitation Training (n=14, mean age=39.3 ± 7.3 months, mental age=20.8±6.6) for 3 hours/week for 10 weeks or control/treatment as usual (n=13, mean age=36.5 ± 8.00, mental age=17.9 ± 7.5).[142, 143] The interventionist-led imitation training included modeling of play and gestures and contingent imitation of children's responses and actions with toys. Children in both arms continued to receive between .25 and 25.5 hours of additional intervention per week. Data for 21 of the children was also reported in an earlier pilot,[143] which reported gains in imitation for the treatment group compared with control ($p<.05$). Gains in imitation were associated with the number of spontaneous play acts at baseline. In the followup RCT,[142] the intervention group made more joint attention initiations compared with control ($p<.05$). Intervention participants also improved on the Social-Emotional Scale compared with the control arm ($p=.02$). Changes in imitation were not shown to be associated with gains in social functioning.

Studies Addressing Parent/Child Communication

In a fair quality randomized trial of a focused play intervention, investigators allocated children to either the play intervention (n=36, mean age=58.3 ± 12.7 months) or a control group (n=34, mean age=55.9 ± 11.9 months).[146] Parents of children in the treatment and the control groups could participate in a parent education program focused on advocacy for their children. Parents in the treatment group also participated in a manualized play time intervention, which used home-based sessions (90 minutes/week for 12 weeks) to promote parental engagement and encouragement of child communication. Children in both groups continued to receive a mean of 14 hours (± 5-8 hours) of school programming and individual services such as ABA-based approaches for a mean of 12 ± 10 to 12 hours/week during the treatment phase. Children also

received a mean of >12 hours of school or individual services during the 12-month followup period.

In analyses at the end of intervention, maternal synchronization (maternal direction of child attention or utterances in line with toys/actions in which child was already engaged vs. redirecting or not synchronized with child's actions) was significantly greater in the treatment group compared with control (effect size=0.08, p<.05). Maternal synchronization was moderated by baseline maternal insightfulness (p<.05) and synchronization was greater in those mothers rated as insightful compared with non-insightful (effect size=0.31, p<.05). Expressive language scores did not differ between groups at the end of intervention or at followup 12 months post-intervention (effect size for baseline to followup change=0.03, p=ns). Children with baseline expressive language abilities below 11.3 months showed greater gains in language in the intervention group vs. control (effect size=0.25 for 24 children with low language skills). The link between short-term gain in maternal synchronization and long-term language (12 months post-treatment) gains was not moderated by maternal insightfulness, nor did initial language skills moderate the link between gains in maternal synchronization after 12 weeks and long term gains in expressive language.[146]

Another fair quality RCT included 14 participants (age range 28 to 68 months, mean 41.14) randomized to either an adapted More Than Words curriculum focused on teaching parents to understand child communication and promote verbal responsiveness or to a waiting list.[144] Treatment group parents received approximately 12 hours of training and 14 small-group parent-child coaching sessions. Overall, children had mean auditory language age of 14.79 months and expressive age of 20.21 months with greater baseline language abilities in the waitlist group compared with the treatment group. At followup, treatment group parents improved significantly compared with the control group in measures of verbal engagement with their children (p values ≤.03). Children in the treatment group increased in prompted communication acts compared with control (p<.03), but spontaneous verbal and nonverbal communication acts did not differ between groups.

Table 9. Summary of outcomes of studies of play/interaction-based interventions

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Months ± SD IQ, Mean ± SD	Key Outcomes
Joint attention studies		
Lawton et al. 2012[147] US **G1:** Immediate joint attention intervention, 9/9 **G2:** Delayed treatment, 7/7 Quality: Fair	**G1:** 46.0 ± 5.00 **G2:** 43.01 ± 6.00 **G1:** 30.3 ± 5.01 **G2:** 33.8 ± 8.74	• Joint attention intervention delivered by preschool teachers • In classroom observations, G1 demonstrated greater initiations of joint attention vs. G2 (effect size=1.85, p<.005) and used more pointing and showing gestures (effect sizes 2.02, 1.85 respectively); no differences in looking or giving • Total joint attention scores on the Early Social Communication Scales did not differ between groups • On intervention exit play observations, no group differences in any joint attention skills • G1 demonstrated less object engagement (effect size=1.41) and more supported engagement (effect size=1.24) compared with G2
Goods et al. 2013[141] US **G1:** Joint attention intervention, 8/6 **G2:** Control, 7/5 Quality: Good	**G1:** 48.73 ± 11.68 **G2:** 54.68 ± 10.25 **G1:** 37.70 ± 15.21 **G2:** 26.67 ± 10.12	• Joint attention intervention delivered by preschool teachers • G1 demonstrated more spontaneous play types, spent less time unengaged in classroom, and initiated more requesting gestures than G2 (effect sizes 0.81, 1.63, 1.51 respectively, p values≤.05) • No significant group differences on the Early Social Communication Scales measures of joint attention
Kaale et al. 2012[145] Norway **G1:** Joint attention intervention, 34/34 **G2:** Control, 27/27 Quality: Fair	**G1:** 47.6 ± 8.30 **G2:** 50.3 ± 8.3 **G1:** 53.3 ± 19.2 **G2:** 59.9 ± 19.7	• Joint attention intervention delivered by preschool teachers • G1 demonstrated more frequent joint attention skills in play with teachers vs. G2, with G1 nearly 5 times more likely to demonstrate initiation of joint attention vs. G2 (effect size=0.44); duration of joint engagement with teachers did not differ between groups • G1 spent longer time in jointly engaged play with mothers vs. G2 post-intervention (effect size=0.67); frequency of joint attention skills with mothers did not differ between groups • Frequency of joint attention measured on the Early Social Communication Scales did not differ between groups • Child age, language age, DQ, or preschool treatment approach did not moderate effects

Table 9. Summary of outcomes of studies of play/interaction-based interventions, continued

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Months ± SD IQ, Mean ± SD	Key Outcomes
Joint attention studies		
Kasari et al. 2012[130, 131, 138, 139] US **G1:** Joint attention intervention, 20/20 **G2:** Symbolic play intervention, 16/16 **G3:** Control, 16/16 Quality: Fair	**G1:** 43.05 ± 6.863 **G2:** 41.41 ± 6.491 **G3:** 41.31 ± 4.542 NR	• Joint attention interventions delivered by interventionists; children in the intervention groups showed greater growth in expressive language, initiation of joint attention, and duration of child-initiated joint attention than did control group children (p=<.01, <.05); receptive language growth not significantly affected by intervention • Amount of intervention services received post-intervention was not related to growth in skills at followup 12 months after the ~6 week intervention, except for child-initiated joint attention: children receiving fewer hours of additional services showed greater growth in child-initiated joint attention • Quality of joint attention (shared positive affect, shared positive affect with utterances) improved in G1 and G2 at 6 an 12 month followups • At followup of 40/58 participants 5-years post-intervention, 32/40 had passing scores on the Expressive Vocabulary Test of spoken language; only baseline play level predicted ability to use spoken language. • Younger age at baseline, initiation of joint attention, and play level were predictors of spoken language ability at 5-year followup • Greater functional play types at baseline predicted better overall cognitive ability at 5-year followup
Kasari et al. 2010[140] US **G1:** Immediate joint attention intervention, 19/19 **G2:** Waitlist control, 19/19 Quality: Good	**G1:** 30.35 ± 0.93 **G2:** 31.31 ± 0.90 **G1:** 64.80 ± 5.35 **G2:** 59.81 ± 3.14	• Joint attention intervention implemented by caregivers • Children in G1 exhibited significantly less object-focused play, responsiveness to joint attention, functional play types, and greater joint engagement than G2 at initial followup (p<.05); gains in joint engagement, responsiveness to joint attention, and types of functional play were maintained at 1-year followup of G1 • Groups did not differ on other/unengaged play time at followup • G1 did not show greater joint attention initiations or diversity of symbolic play compared with G2 • Greater caregiver quality of involvement predicted increased joint engagement
Pretend play studies		
Murdock et al. 2011[148] US **G1:** Pretend play intervention, 6/6 **G2:** Comparison, 6/6 Quality: Poor	**G1:** 69.33 ± 5.9889 **G2:** 62.17 ± 6.2102 NR	• Intervention included typically developing peers as play models • Both groups gained play dialog skills from baseline to followup (p=.003), with greater gains in G1 vs. G2 (260% vs. 136%, p=.041) • Participants were able to generalize play dialog skills to a toy not used in the intervention (p=.012) with an increase in play dialog utterances

Table 9. Summary of outcomes of studies of play/interaction-based interventions, continued

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Months ± SD IQ, Mean ± SD	Key Outcomes
Imitation studies		
Ingersoll. 2010[142, 143] US **G1:** Reciprocal imitation training, 15/14 **G2:** Control, 14/13 Quality: Good	**G1:** 41.36 ± 4.30 **G2:** 37.20 ± 7.36 NR	• Pilot evaluation of a reciprocal imitation training program • G1 made greater gains in spontaneous and prompted imitation, object imitation, gesture imitation, initiation of joint attention, and on the Social-Emotional Scale than G2 (p values ≤.05) • Number of spontaneous play actions associated with gains in spontaneous imitation and gesture imitation (p<.05) • Changes in imitation skills not associated with social functioning changes in mediation analysis
Parent-child communication studies		
Siller et al. 2013[146] US **G1:** Parental responsiveness intervention, 36/31 **G2:** Control, 34/31 Quality: Fair	**G1:** 58.3 ± 12.7 **G2:** 55.9 ± 11.9 NR	• Intervention focused on increasing parents' responsiveness to child communication • Mothers of children in G1 demonstrated greater synchronization with child communication vs. G2 (p<.05, effect size=0.08) • No significant effects of intervention on expressive language • Mothers rated as more insightful at baseline had greater gains in synchronization
Venker et al. 2011[144] US **G1:** Parental responsiveness intervention, 7/7 **G2:** Delayed treatment, 7/7 Quality: Fair	**G1+G2:** 41.14 ± 10.40 NR	• Intervention targeting parents' verbal responsive and engagement with child play • Both groups increased prompted communication acts from baseline to followup; in between group comparisons, G1 had greater increases vs. G2 (p<.03) • Number of children increasing spontaneous communication acts did not differ between groups

DQ-developmental quotient; G-group; IQ-intelligence quotient; N-number; NR-not reported; SD-standard deviation

Behavioral Interventions Focused on Associated Behaviors

Key Points

- Five good quality and one fair quality studies evaluated the effects of cognitive behavioral therapy (CBT) on behaviors associated with ASD.
- CBT improved anxiety symptoms and effects were maintained over time in 4 of the 5 studies. The one study that did not show significant benefit compared with control group demonstrated an improvement in anxiety symptoms in the CBT group; however, it was not greater than that seen in the control group. This study was also the only study to use an active control (social recreational therapy) rather than a waitlist or treatment as usual control.
- Two RCTs demonstrated significant positive effects of CBT on socialization.
- One small RCT rated as fair demonstrated improvement in emotion regulation after treatment with CBT.

- In a large good quality RCT, augmentation of risperidone with parent training produced more significant improvement in adaptive behavior, socialization and communication than risperidone alone, but effects were not maintained after one year.

Overview of the Literature

We identified nine comparative studies addressing interventions targeting conditions/behaviors commonly associated with ASD in the 2011 review. These studies included four RCTs[150-154] and one nonrandomized trial[155] of fair quality and three RCTs[156-158] and one prospective cohort[159] of poor quality. Studies addressed CBT for anger or anxiety or parent training approaches. In addition to these studies, we identified seven new studies (reported in 12 publications);[152-154, 160-168]two of these seven studies, one evaluating CBT[152, 153, 165] and one assessing parent training plus risperidone,[154, 166-168]report on populations addressed in studies in the 2011 review. As in the 2011 review, studies address either CBT or parent training modalities (Table 10).

Among the seven studies identified for the current review, six RCTs evaluated CBT: five conducted in the United States[160, 162-165] and one in Singapore.[169] Two studies examined CBT compared with control groups receiving treatment as usual.[160, 164] Three studies examined CBT compared with wait listed controls,[152, 153, 162, 163, 165] and one study compared CBT with social recreational therapy.[161] Studies included two populations: four studies included subjects with both ASD and primary anxiety disorder diagnoses,[152, 153, 160, 163-165]and two studies included subjects with ASD only (did not report whether or not subjects had a formal diagnosis of primary anxiety disorder).[161, 162] Outcomes measured included improvements in anxiety alone in four studies,[160, 161, 163, 164] improvements in anxiety and daily living skills in one study;[152, 153, 165] and improvements in emotion regulation in one study.[162]
Subjects ranged in age from 4 to 16 years. Five study interventions were conducted over 16 weeks,[152, 153, 160, 161, 163-165]and one study intervention was carried out over 9 weeks.[162] We rated five studies as good quality[152, 153, 160, 161, 163-165] and one as fair.[162]

We identified one fair quality RCT reported in multiple publications and addressing parent training approaches (also reported in the 2011 review).[154, 166-168]The study examined the utility of augmenting risperidone with parent training vs. risperidone alone for treatment of serious behavior problems and irritability. Children had diagnoses of ASD in addition to serious behavior problems as defined by reaching specific cutoff scores on measures of irritability and problem behavior, and ages ranged from 4 to 13 years. Outcomes measured included measures of adaptive behavior in addition to measures of problem behavior and irritability.

Detailed Analysis

Most studies investigating CBT as the primary intervention identified anxiety as the target symptom. One good quality RCT measured changes in anxiety symptoms in addition to core ASD symptoms.[164] The study included 36 children ages 7 to 11 with both ASD and primary anxiety disorder diagnoses. Subjects were randomized to an intervention group receiving 16 weekly CBT sessions or a control group receiving treatment as usual. There were no group differences with the exception of slightly higher proportion of subjects with Autistic Disorder compared with PDD or Asperger's in the intervention group. Primary outcome measures included the following measures of anxiety; Pediatric Anxiety Rating Scales (PARS), Anxiety Disorders Interview Schedule-IV-Child/Parent Version and Clinical Global Impressions-Severity (CGI-S). Secondary outcome measures included other measures of anxiety such as the

Multidimensional Anxiety Scale for Children-Parent Version and Child Behavior Checklist, a measure of social responsiveness, the Social Responsiveness Scale, and the Columbia Impairment Scale-Parent Version, which assesses interpersonal, social and academic skill. All measures were collected at baseline, the end of the intervention and 3 months following termination of the intervention. At the end of the intervention, large treatment effects were observed in all primary outcome measures. Pediatric Anxiety Scale ratings were reduced by 21 percent in the CBT group vs. 9 percent in the control group. CGI-S scores were more improved in the CBT group than the control group (effect size 1.06, $p<0.01$). On the blinded, clinician-rated Anxiety Disorders Interview Schedule, 38 percent of CBT participants vs. 5 percent of control participants showed clinical remission of anxiety symptoms (effect size 1.37, $p=0.01$). Scores on all measures did not change significantly between the end of intervention and the 3-month followup evaluation. Among secondary outcome measures, group differences were observed with greater improvements on the Columbia Impairment Scale, internalizing symptoms on the Child Behavior Checklist, Revised Children's Manifest Anxiety Scale anxious arousal subscale, total score and social communication and social mannerisms subscales on Social Responsiveness Scale. No group differences were observed on externalizing symptoms of the Child Behavior Checklist, dysphoric mood, oversensitivity and worry subscales of the Revised Children's Manifest Anxiety Scale, or social awareness, social cognition and social motivation subscales of the Social Responsiveness Scale.

Another good quality RCT assessed a CBT-based intervention specifically developed for children with ASD ("Facing Your Fears").[160] The study included 48 children ages 7 to14 with ADOS-confirmed diagnosis of ASD randomized to either the CBT group or treatment as usual. Participants were required to be able to speak in full complex sentences and have clinically significant symptoms of anxiety measured on the Screen for Child Anxiety and Related Emotional Disorders-parent version (SCARED). No group differences were identified relative to age, IQ, sex, parents' marital status, mother's education, ethnicity, specific ASD diagnosis, or use of psychiatric medications. The intervention consisted of 12 multifamily group sessions over 4 weeks following the manualized CBT treatment. The Anxiety Disorders Interview Schedule for Children was performed at baseline and again at the end of the intervention. The CGI-S scale was obtained at the end of intervention. Independent Clinical Evaluators (ICEs) blinded to the participant's condition assigned DSM-IV diagnoses and provided summary codes of clinical severity and interferences called Clinician Severity Ratings. Group differences in severity ratings were noted for all anxiety diagnoses with medium to large effect sizes. The overall number of anxiety disorders at followup was significantly reduced in the intervention group, and there was a large effect size noted in the reduction of generalized anxiety disorder diagnoses. There were no group differences noted in diagnostic status for other anxiety diagnoses. Significant improvement was noted on the CGI-S in the intervention group as compared with the control group (effect size 1.03 and $p=0.003$). The SCARED was repeated at 3 and 6 months for the intervention group and indicated that reduction in anxiety symptoms had been maintained.

A third good quality RCT investigated the effects of the Coping Cat CBT program on anxiety symptoms in 22 children ages 7 to 14 with diagnosis of ASD and at least one primary anxiety disorder.[163] Twelve children were assigned to the intervention group and the remaining 10 children were enrolled as waitlisted controls. There were no baseline group differences with the exception of more children in the control group receiving stimulant medications. The intervention consisted of 16 weekly 60 to 90 minute CBT sessions following the Coping Cat treatment manual. Anxiety measures were repeated just after completion of the intervention and

again at 2 months after completion of treatment. At the completion of the intervention, 58 percent of the intervention group compared with 0 percent of the control group no longer met criteria for a primary anxiety disorder (p=0.003). Spence Children's Anxiety Scale ratings improved significantly in the intervention group (34.92 to 20.08) but not in the control group (32.3 to 31.7) (p=0.02). Co-morbid diagnoses decreased in the intervention group compared with control group from baseline to end of intervention (p<0.001). After 2 months, four of 11 intervention group participants continued to not meet requirements for anxiety disorder diagnosis. The authors reported a number needed to treat for the intervention of 1.72.

A good quality RCT conducted in Singapore compared the effects of CBT to an established social recreational intervention on anxiety symptoms.[161] Seventy children with ASD diagnoses, verbal IQ>80, and perceptual reasoning IQ>90 were randomly assigned to the CBT group (n=36) or social recreational group (n=34). The CBT group had slightly higher verbal IQ (100.25 in CBT group compared with 93.06 in social recreational group), otherwise there were no significant differences between groups. The CBT group underwent 16 weekly 90 minute small group CBT sessions. The social recreation group underwent 16 weekly 90 minute small group sessions following a manualized treatment protocol that included activities aimed at independent living, self-engagement, motor coordination, intellectual stimulation and socialization. The Spence anxiety scale and CGI-S were repeated at the end of treatment, 3 months and 6 months after the end of treatment. Both groups demonstrated reduction in anxiety on the Spence scale between baseline and at 6-month followup; however, only the social recreational group demonstrated reduction in anxiety immediately following intervention. CGI-S scores improved over time for both groups, but group differences at final followup were not significant.

One good quality RCT reported in multiple publications[152, 153, 165] examined the effects of the Building Confidence CBT program adapted for children with ASD on anxiety symptoms, daily living skills, and, in a subgroup of children, socialization. Forty children ages 7 to 11 with ASD and separation anxiety, social phobia, or obsessive-compulsive disorder and IQ >70 were randomized to the CBT group or to waitlist control group. No group differences were noted with the exception of more children in the CBT vs. control group having comorbid diagnosis of major depressive disorder or dysthymia (18% vs. 0%, respectively). The intervention consisted of 16 weekly 60-90 minute CBT sessions. Assessments of anxiety included the Anxiety Diagnostic Interview Schedule, the Multidimensional Anxiety Scale for Children parent and child reports, and the Clinical Global Impressions-Improvement (CGI-I) scale. Measures of daily living skills included the Vineland and the Parent Child Interaction Questionnaire, which assesses the level of parent involvement in daily living skills. Socialization was measured with the Social Responsiveness Scale in a group of 19 children from the early stages of recruitment. Most measures were repeated at baseline, at the end of the intervention and, for 10 intervention participants who were still available, at 3 months after the end of intervention. The CGI-I was only collected at the end of intervention and at the 3-month followup. At the end of intervention, 92.2 percent of the intervention group met criteria for positive treatment response based on CGI-I and 64.3 percent no longer met criteria for any anxiety disorder on the Anxiety Disorders Interview Schedule, compared with only 9.1 percent demonstrating positive treatment response on the CGI-I and (p<0.0001) and 9.1 percent no longer meeting criteria for anxiety disorder in the control group (p<0.0001). Overall this data did not change significantly at the three-month followup period. The MASC scores were significantly lower in the intervention group vs. the control group at followup (p<0.0001) for the parental report however the child report did not demonstrate significant differences. This data also did not change significantly at the 3-month

followup period. Vineland total daily living and personal daily living raw scores significantly improved for the intervention vs. the control group ($p<0.05$) with effect sizes of 0.45 for total daily living skills and 0.50 for personal daily living skills. Unnecessary parental involvement and parental involvement in child self-care were significantly reduced in the intervention vs. control groups ($p<0.05$ and $p<0.01$ respectively). Treatment effects on the Vineland and parental intrusiveness scales were maintained at 3 months post intervention in the 10 children for whom followup data were available. Among those participants receiving the Social Responsiveness Scale, differences favoring the intervention group were found on three of the five subscales including social communication, social motivation and social awareness ($p<0.05$).

A small, fair quality pilot RCT examined the utility of CBT to improve emotion regulation in a young group of 11 verbal children ages 5 to7 years.[162] Children randomized to the intervention group (n=5) underwent 9 weekly 60 minute sessions of CBT focusing on skill-building, stress management and understanding expression of emotions. The remaining 6 children were randomized to a waitlist control group. This study reported demographic data for all participants but did not present data regarding potential differences between groups. Measures of the child's capacity for emotion regulation was assessed through his report of number emotion regulation strategies that might be used during the reading of a vignette, parental report on an emotion regulation scale, parent observation and notation of frequency and duration of anger/anxiety episodes, and parent report of their own self-confidence and confidence in their children's abilities to handle emotions. Measures were collected at baseline and at the end of intervention. At the end of intervention children in the CBT group reported a greater number of emotion regulation strategies in response to the vignettes (4 vs. 1.29 in control group $p<0.05$, effect size 0.65) and parents had greater confidence in their ability to manage child's anger and greater confidence in the child's ability to manage their own anger ($p<0.05$, effect sizes 0.84 to 0.89).

One fair quality RCT (reported in multiple publications) assessed a parent training approach (treatment with risperidone alone vs. risperidone augmented with a parent-training program) to improving adaptive behavior and communication and socialization skills.[154, 166-168] The parent training program included 11 core sessions, one home visit and up to three optional sessions during the first 16 weeks, followed by four booster sessions over the next 8 weeks. The training focused first on antecedents, purpose, and reinforcements of problem behaviors and then on teaching parents management strategies for these behaviors. Investigators recruited 124 children ages 4 to 14 years with ASD, severe problem behaviors evidenced by positive scales on the Aberrant Behavior Checklist-Irritability subscale and CGI-S subscales, and IQ>35. Forty-nine participants were randomized to risperidone plus parent training intervention group and 75 to the risperidone alone control group. No group differences were observed with the exception of slightly higher ABC-irritability subscale scores in the intervention group.

The Aberrant Behavior Checklist, Vineland, and the Home Situations Questionnaire were completed at baseline, at 24 weeks after completion of intervention and, for the Aberrant Behavior Checklist and Home Situations Questionnaire, one year after intervention. At 24 weeks, scores on the Home Situations Questionnaire demonstrated decreased severity in more children in the intervention group vs. control ($p<0.006$), and greater improvements were noted in the intervention group on the Aberrant Behavior Checklist Irritability ($p=0.01$), Stereotypic behavior, ($p=0.04$) and Hyperactivity ($p=0.04$) subscales compared with the control group. Also at 24 weeks post intervention, greater improvements in the intervention group were noted on Vineland socialization ($p=0.01$) and adaptive composite ($p=0.05$) standard scores and on Vineland noncompliance ($p=0.03$), socialization ($p=0.03$) and communication ($p=0.05$) age

equivalent scores. These treatment gains were not associated with IQ or adaptive or maladaptive behaviors. Analysis indicated higher baseline Home Situations Questionnaire scores predicted greater improvement regardless of treatment (p=0.007). Authors also analyzed 21 potential moderator variables and none significantly moderated Home Situations Questionnaire or Aberrant Behavior Checklist-Hyperactivity scores, suggesting that parent training may be effective for a range of children. At 1-year followup, data was available for 87 participants. Group differences at one year on the Home Situations and Aberrant Behavior Checklist were no longer significant. Data was not available for Vineland at one-year followup.[154, 166-168]

Table 10. Summary of outcomes of studies of interventions targeting conditions commonly associated with ASD

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
CBT Studies		
Storch et al. 2013[164] US **G1:** CBT, 24/22 **G2:** Usual care, 21/21 Quality: Good	**G1:** 8.83 ± 1.31 **G2:** 8.95 ± 1.40 NR	• Significantly greater improvements in all primary outcomes for G1 compared with G2; effect sizes ranged from 0.84 to 1.06 • Pediatric Anxiety Rating Scale ratings were reduced by 29% for G1 vs. 9% for G2 (effect size=1.03, p<.01) • CGI-S improved from a mean 3.50 for G1 at baseline to 2.67 at followup compared with baseline mean of 4.00 and followup of 3.57 for usual care (effect size=1.06, p<.01) • On the blinded, clinician-rated Anxiety Disorders Interview Schedule, 38% (9/24) G1 participants vs. 5% (1/21) G2 participants achieved clinical remission of anxiety symptoms (effect size=1.37, p=.01) • At followup of G1 three months post-treatment, 11/15 maintained treatment response and 6/9 maintained remission (p=NS); scores on the CGI-S, Anxiety Disorders Interview Schedule, and Pediatric Anxiety Rating Scale did not change significantly from end of treatment
Keehn et al. 2013[163] US **G1:** CBT, 12/12 **G2:** Wait list control, 10/10 Quality: Good	**G1:** 11.65 ± 1.41 **G2:** 11.02 ± 1.69 **G1:** 108.42 ± 17.70 **G2:** 110.40 ± 17.39	• On blinded, clinician-rated Anxiety Disorders Interview Schedule, 58% of G1 no longer met criteria for primary anxiety diagnosis at followup; 100% of G2 still met criteria (p=.003) • Parent-reported Spence Children's Anxiety Scale ratings improved over time for G1 compared with G2 (baseline means: G1=34.92, G2=32.20; at followup G1=20.08, 31.70, p=.02) • Co-morbid diagnoses decreased in G1 compared with G2 from baseline to followup (p<.001) • 4/11 treatment group participants with 2-month post-treatment followup data continued not to meet criteria for anxiety diagnosis • NNT=1.72

Table 10. Summary of outcomes of studies of interventions targeting conditions commonly associated with ASD, continued

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
CBT Studies		
Reaven et al. 2012[160] US **G1:**CBT**,** 24/21 **G2:** Usual care, 26/26 Quality: Good	**G1:** 125.75 months ± 21.47 **G2:** 125.00 months ± 20.45 **G1:** 107.08 ± 16.85 **G2:** 102.23 ± 17.33	• Blinded clinician severity ratings significantly reduced from baseline for all anxiety diagnoses in G1 compared with G2; effect sizes ranged from medium to large • Significant reduction in overall number of anxiety disorders in G1 compared with G2 at followup; large effect size for reduction in generalized anxiety disorder diagnoses (effect size=0.85) but no significant between group differences in diagnostic status for other anxiety diagnoses • 50% of G1 and 8.7% of G2 had clinically meaningful improvement in anxiety symptoms on the CGI-S (effect size=1.03, p=.003) • At 6 month post-intervention followup for G1, parent and child SCARED scores suggested maintenance of reduction of anxiety symptoms
Sung et al. 2011[161] Singapore **G1:** CBT, 36/36 **G2:** Social recreational program, 34/34 Quality: Good	**G1:** 11.33 ± 2.03 **G2:** 11.09 ± 1.53 **G1:** 100.25 ± 13.97 **G2:** 93.06 ± 12.81	• Both groups reported reductions in anxiety from baseline to end of treatment; reports of panic attacks were significantly reduced from baseline in G2 (p<.01); differences between groups at final followup (6 months post-treatment) were not significant • CGI-S scores improved over time in both groups, but between group differences at final followup were not significant
Drahota et al. 2011[152, 153, 165] US **G1:** CBT, 17/14 **G2:** Wait list control, 23/22 Quality: Good	**G1:** 9.18 ±1.42 **G2**: 9.22 ±1.57 NR	• 92.9% of G1 met criteria for positive treatment response; 64.3% of G1 no longer met criteria for any anxiety disorder on the Anxiety Disorders Interview Schedule • Multidimensional Anxiety Scale for Children scores were significantly lower (i.e., reduction in anxiety) in G1 vs. G2 at followup (p<0.0001) with maintenance of response for G1 at followup 3-months post-intervention • Vineland total daily living and personal daily living raw scores significantly improved for G1 vs. G2 at followup (p≤.05); effect sizes were 0.45 (total daily living skills) and 0.50 (personal daily living skills) • Mean age equivalency for total daily living skills increased from 5.2 years at baseline to 6.0 for G1 and from 5.4 years at baseline to 5.7 for G2; for personal daily living skills, mean age equivalency increased from 4.1 to 5.0 years in G1 and 4.5 to 4.6 years in G2 • Unnecessary parental involvement and parental involvement in child self-care were significantly reduced in G1 vs. G2 (p<.05, p<.01 respectively) • Treatment effects on the Vineland and parental intrusiveness scales were maintained at followup 3-months post-intervention for 10 children with followup data

Table 10. Summary of outcomes of studies of interventions targeting conditions commonly associated with ASD, continued

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
CBT Studies		
Scarpa et al. 2011[162] US **G1:** CBT, 5/5 **G2:** Delayed treatment control, 6/6 Quality: Fair	**G1+G2 (range):** 5-7 years **IQ:** NR	• Pilot study to assess utility of CBT approach to improve emotion regulation (Sofronoff, 2005, 2007) in younger children • G1 articulated significantly greater number strategies in response to vignettes than G2 (mean 4 vs. 1.29, p<.05, effect size=0.65) • Greater parental confidence in own ability to manage child's anger and greater confidence in child's ability to manage anger and anxiety in G1 vs. G2 (p<.05, effect sizes=0.84 tob0.89)
Parent Training Studies		
RUPP 2012[154, 166-168] **G1:** Risperidone, 49/36 (1-yr followup) **G2:** Risperidone+Parent training, 75/51 (1-yr followup) Quality: Fair	**G1:** 7.5 ± 2.80 **G2:** 7.38 ± 2.21 IQ > 70, n (%) **G1:** 23 (46.9) **G2:** 46 (63) IQ<70, n(%) **G1**: 26 (53.1) **G2:** 27 (37)	• After 24 weeks of treatment, significant group by time interaction on the Home Situations Questionnaire (HSQ) (p<0.006); HSQ scores declined (i.e., decreased severity) in more children in G2; Aberrant Behavior Checklist (ABC) irritability, stereotypic behaviors, hyperactivity subscales all showed significant group differences over time with less severe symptoms in each of the domains in G2 • After 24 weeks, Vineland socialization and adaptive composite standard scores and socialization, noncompliance, and communication age equivalent scores were significantly better in G2 vs. G1 (p≤.05, effect sizes ranging from 0.14 to 0.35); treatment gains were not associated with IQ or adaptive or maladaptive behaviors • Higher baseline HSQ scores predicted greater improvement regardless of treatment (p=.007); effect size of 0.81 (p<.01) for those with greater severity • Of 21 potential moderator variables (e.g., child age, maternal education) none significantly moderated HSQ or ABC-Hyperactivity scores, suggesting that parent training may be effective for a range of children • At followup of 87 participants 12-months post-intervention, between group differences on the HSQ or ABC were no longer significant

ABC-Aberrant Behavior Checklist; ASD-autism spectrum disorder; CBT-cognitive behavioral therapy; CGI-Clinical Global Impression; G-group; HSQ-Home Situations Questionnaire; IQ-intelligence quotient; N-number; NR-not reported; RUPP-Research Units on Pediatric Psychopharmacology; SCARED-Screen for Child Anxiety Related Disorders; SD-standard deviation

Other Behavioral Interventions

Key Points

- In one study comparing CBT plus melatonin to either melatonin or CBT alone, all participants improved on measures of sleep quality, with the combination group generally improving more than the others.
- One small, short-term study of a sleep education pamphlet for parents demonstrated little positive effect of the pamphlet.
- Small, short-term studies of neurofeedback reported some improvements on parent-rated measures of communication and tests of executive function

Overview of the Literature

We classified studies not cleanly fitting in any of the other categories as "other." In addition to two poor quality RCTs targeting neurofeedback[170, 171]and described fully in the 2011 review, we identified four new studies (five publications) evaluating interventions targeting sleep behaviors[172, 173] and neurofeedback (Table 11).[174-176]We considered one RCT comparing the effects of CBT with or without melatonin with placebo on sleep habits as fair quality,[173] one RCT evaluating the effects of sleep education pamphlet as fair quality,[172] and two studies (reported in three publications)[174-176]of neurofeedback as fair[174] and poor[175, 176] quality. Studies were conducted in Europe[173-176] and the United States[172] and included 204 total participants with ages ranging from 2 to 12 years.

Detailed Analysis

One fair quality RCT compared CBT alone, melatonin alone, CBT plus melatonin, and placebo in 160 children with ASD between the ages of 4 and 10 years.[173] CBT consisted of four 50-minute sessions focused on recognizing dysfunctional attitudes about sleep, parent-management of children's sleep, and replacing poor sleep habits with appropriate behavior. Participants received 3 mg controlled release melatonin administered at the same time each day. Investigators allocated 40 participants to each group; mean age across groups ranged from 6.3 to 7.1 years, and each group lost 5 to 8 participants over the 12-week intervention due to withdrawals or missing actigraphy data. All active treatment groups improved in most measures of sleep quality compared with the control group ($p<.01$). In general, the combination group improved more than the others, followed by the melatonin alone and CBT alone groups. Scores for children who received melatonin alone improved on bedtime resistance, sleep onset delay, sleep duration, and night waking compared with the CBT group ($p<.001$). Effect sizes (exact data not reported) ranged from medium to high. Sleep onset latency (time to fall asleep) and sleep efficiency (ratio of total sleep time to total time in bed) were reduced by 50 percent (sleep latency) or 85 percent (efficiency) in 85 and 63 percent of children in the combination group and 39 and 46 percent of children in the melatonin group, respectively. In the CBT arm, 10 percent of children met each criterion, and no children in the control arm achieved these percentages of reduced latency or improved efficiency. The study reported no significant harms.

One RCT evaluated the effects of a sleep education pamphlet compared with no intervention in 36 children with ASD between the ages of 2 and 10 years.[172] Parents of children in the intervention group received a four-page pamphlet with information about sleep environment, promoting bedtime routines and schedules, teaching children to fall asleep alone, avoiding naps where possible, and promoting a sleep/wake schedule; parents did not receive additional

instruction. At the 2-week followup, groups did not differ significantly on sleep latency, waking after sleep onset, total sleep time, or sleep fragmentation. Sleep efficiency (total sleep time/time in bed) improved slightly in the intervention group (baseline mean 75.5% ± 6.1, followup 77.8% ± 7.0 vs. baseline mean of 76.8% ± 6.0, followup 75.1% ± 6.7 for the control group, p=.04).

In a nonrandomized trial including 14 high functioning children with PDD-NOS (IQ≥70) investigators assigned children to 40 sessions of neurofeedback (n participants=7, mean age=9.63 ± 1.53 years) sessions designed to treat individuals with ADHD or to a wait-list control group (n=7, mean age=10.64 ± 1.41 years).[176, 177] Electroencephalogram data did not differ significantly between groups at followup; however, the treatment group improved on some executive function measures (auditory selective attention, inhibition of verbal responses and impulsive tendencies, all p<.05) and in nonverbal communication compared with the control group. Cognitive flexibility and goal setting improved for the treatment group vs. control but ability to recognize words did not. Parents of children in the treatment arm also rated their children's communication skills as improved following neurofeedback training. In analyses combining data for the treatment and control group participants who went on to complete neurofeedback training (n=NR) conducted 12 months after treatment, gains in auditory selective attention, non-verbal communication, and parent measures of social behavior continued.

In an RCT evaluating neurofeedback, 10 children (mean age=9.43 ± 1.44 years) received 40 neurofeedback sessions aimed at decreasing theta power in the frontal and central brain areas. Ten children served as controls (mean age=9.14 ± 1.34 years).[174] In contrast to the prior neurofeedback study, children had diagnoses across the ASD spectrum, treatment occurred in school and at home, and both parents and teachers completed outcome questionnaires. Immediately after treatment, theta activity was reduced in 60 percent of the intervention group. Social behavior, especially reciprocal social interaction, as measured on the parent-rated Social Communication Questionnaire, improved for the treatment group compared with control (p<.05) as did scores on the Children's Communication Checklist and on the set-shifting domain of executive function (p<.05). Scores on other domains of executive function did not differ between group nor did scores on teacher-rated measures. At followup 6-months post-treatment, the intervention group showed continued improvement on parent-rated measures of social behavior, communication, and repetitive behavior as well as set-shifting compared with the control arm (p<.05) Parents were not blinded to treatment condition.

Table 11. Summary of outcomes of behavioral--other studies

Author, Year, Country Groups, N Enrollment/N Final Study Quality	Age, Mean Years ± SD IQ, Mean ± SD	Key Outcomes
Cortesi et al. 2012[173] Italy **G1:** Melatonin+CBT, 40/35 **G2:** Melatonin alone, 40/34 **G3:** CBT alone, 40/33 **G4:** Placebo, 40/32 Quality: Fair	**G1:** 6.4 ± 1.1 **G2:** 6.8 ± 0.9 **G3:** 7.1 ± 0.7 **G4: 6.3** ± 1.2 NR	• G1, G2, and G3 improved in measures of sleep compared with G4 (p<.01), with G1 improving more than the others, though not significantly • On actigraphy measures, G1 improved more than G2 and G3 • Primary effects of CBT alone were on sleep latency and sleep anxiety
Adkins et al. 2012[172] US **G1:** Sleep education pamphlet, 18/18 **G2:** No intervention, 18/18 Quality: Fair	**G1+G2:** 6.4 ± 2.6 **G1:** 75.1 ± 25.5 **G2:** 85.6 ± 27.1	• No between group differences in sleep latency, waking after sleep onset, total sleep time, or sleep fragmentation at the 2 week post-intervention followup • Sleep efficiency improved somewhat in G1 vs. G2 (p<.04)
Kouijzer et al. 2009[176, 177] US **G1:** Neurofeedback, 7/7 **G2:** Control, 6/6 Quality: Poor	**G1:** 9.63 ± 1.53 **G2:** 10.64 ± 1.41 **G1:** 92.5 ± 16.05 **G2:** 93.83 ± 13.67	• Improvements in some measures of executive function in G1 vs. G2 (p<.05) • Improvements in nonverbal communication and parent-rated communication and behavior measures in G1 vs. G2 • Analyses combining groups (G1 and some G2) suggested maintenance of improvement in social behavior
Kouijzer et al. 2009[174] US **G1:** Neurofeedback, 10/10 **G2:** Control, 10/10 Quality: Fair	**G1:** 9.43 ± 1.44 **G2:** 9.14 ± 1.34 **IQ:** NR	• Parent-rated scores in reciprocal social interaction and communication improved for G1 vs. G2 (p<.05) • Set-shifting skills improved for G1 vs. G2 (p=.045) • Parent-rated measures at 6 months post-treatment suggested maintenance of improvements in communication and set-shifting for G1

CBT-cognitive behavioral therapy; G-group; IQ-intelligence quotient; NR-not reported; SD-standard deviation

KQ2. Modifiers of Treatment Effects

Understanding the degree to which child characteristics (i.e., specific ASD-related difficulties and skills), treatment factors (e.g., type, duration, intensity), and systems (e.g., family, community) influence response to treatments could improve targeting of treatments to the appropriate children and circumstances. Nineteen papers (described in multiple publications) reported predictor, moderator, or mediator data;[71, 75, 76, 78, 80-83, 85, 86, 89, 91, 93, 96, 98, 99, 103, 116, 117, 125, 142, 143, 146, 154, 166-168] however, not all studies may have been adequately designed or powered to assess modifiers of effects.

Child-Related Factors

Age

As in the 2011 review, several studies reported associations between age at intake and improved outcomes. In early intervention studies, younger age was typically associated with greater improvements: greater language gains were seen in children who were younger with lower functioning levels at baseline in one RCT of an approach incorporating parent training.[71,

[103] Another study assessing parent-delivered ESDM reported greater increases in developmental quotient scores in children under 24 months of age in analyses combining the ESDM group with the control group, which received community-based treatment (effect size=-1.20, p=.002).[96]

Age effects were not consistent, however, and may reflect characteristics of subgroups and treatment characteristics that need further elucidation. For example, one study comparing preschool-delivered intensive early intervention and treatment as usual reported larger adaptive behavior gains for older children in the early intervention group.[76] Another RCT comparing early intensive treatment delivered by parents and by specialized center staff with eclectic treatment and identified predictors of progress: in the parent training group, older children achieved better adaptive behavior outcomes; younger children made more gains in early language comprehension and production. Children who gained more language comprehension had higher adaptive behavior scores pre-treatment. Pre-treatment language comprehension also predicted post-treatment language production. In the eclectic group, higher pre-treatment mental development state and early language skills predicted better outcome on parent-reported adaptive behaviors. Initial higher adaptive behaviors predicted better post-treatment early language comprehension. In both groups, child outcomes on early language skills, mental developmental state, and adaptive behaviors were significantly influenced by self-reported parental stress, children's ability to respond correctly to prompts, the number and difficulty of treatment targets, and children's problem behaviors in sessions. Children who were perceived by their parents as more difficult had less improvement in autism severity.[99, 100]

In a retrospective cohort study of a community-based early intervention program, outcomes were related to age at enrollment, treatment duration, and higher baseline adaptive scores. A significant interaction emerged between age at enrollment and group membership, with younger starting age influencing outcomes for the treatment group but not the waitlist control.[85] In contrast to the early intervention studies, in an RCT assessing emotion recognition, older age was correlated with improved identification of fear expressions, affect recognition, and the mind reading desire based task.[116] Another RCT of a preschool-based joint attention intervention compared an 8-week treatment program focused on increasing initiating, giving, and sharing joint attention skills plus preschool to preschool alone in 61 children with ASD.[145] In exploratory analyses, investigators found no putative moderators (age, developmental quotient, language age, program philosophy) to be significant, suggesting that the intervention may be applicable across developmental levels.

IQ/Cognition

Associations of outcome and IQ or measures of cognition were mixed across studies. Intervention efficacy was associated with baseline cognitive scores in one early intervention study comparing preschool models classrooms,[82] with higher baseline cognitive scores associated with less improvement. In an early intervention prospective cohort study, baseline IQ was positively correlated with socialization, communication, daily living, and composite score gains on the Vineland in the treatment group; however, baseline IQ did not correlate with IQ at followup.[76] In a study assessing emotion recognition, higher verbal IQ was associated with some short term improvements in fear recognition and mind reading tasks,[116] while in another emotion recognition RCT, IQ was not correlated with improved outcomes in either the treatment or control groups.[125] In another RCT of a group-based social skills approach, IQ was not associated with response status;[117] similarly, treatment gains were not associated with IQ in an RCT comparing parent training plus risperidone to risperidone alone.[154, 166-168]

ASD Severity/Symptom Severity and Diagnoses

In some studies, children with lower symptom severity or less severe diagnoses improved more than participants with greater impairments. In an RCT assessing ABA-based early intervention, lower baseline autism severity was associated with parent-reported cognitive and adaptive growth for children who received eclectic vs. ABA intervention, but not with standardized test scores.[80, 81] A prospective cohort study of preschool-based early intensive intervention reported that children in the early intervention group with PDD-NOS or Asperger diagnoses (but not autism) had greater gains in overall adaptive behavior, communication, and daily living skills.[76] A prospective cohort study comparing four early intervention approaches (home-based 1:1 ABA intervention, low intensity home-based programming for children with special needs [portage], home-based, local health authority-developed intervention incorporating parent training, and special education nursery/preschool) evaluated relationships between ASD severity, time in intervention, and effectiveness of intervention.[93] Hours of intervention ranged from 2 to 40 across groups, with the home-based ABA group receiving the most (mean 30.4/week) and the Portage group the least (mean 8.5/week). Baseline autism severity and total intervention hours modified effects of treatment significantly. First, baseline ASD severity was inversely related to composite change scores for all but the home-based ABA group and was positively related in that group. That is, children with more severe autism symptoms made more progress in ABA and less in the other intervention groups. Second, more intervention time was negatively related to composite change scores for children in ABA but not in the other groups. More hours of ABA were associated with less progress relative to school enrollment or other home-based interventions.

Two reports[87, 89] including participants in a retrospective cohort study evaluating an early intervention approach[85] plus additional participants assessed potential outcome predictors including baseline age, Vineland scores, IQ, and ASD severity (CARS). Younger age at intake, higher initial developmental levels[89] and treatment intensity[87, 89] were related to better treatment outcomes. Vineland standard scores and IQ and mental age were higher for the 32 children whose followup standard scores on cognitive and/or adaptive behavior were in the low average range or better (>85) and whose CARS scores were in or very close to the non-autism range (<30), Similarly, intake CARS severity was significantly lower, and "average outcome" children began intervention earlier (mean 42 months vs. 55 for rest of sample) and received intervention for a longer duration. More of these children also had diagnoses of PDD-NOS. Children who had poor outcomes at followup (n=75) had statistically significantly lower IQ , mental age, rate of development, and Vineland scores (except for the socialization domain), with p values ranging from .01 to <.001. Differences likely were not clinically significant, however, and diagnostic category, severity, age at entry, and duration of therapy were not significantly different in the poor outcome group compared with the rest of the sample.

In an RCT evaluating an emotion recognition intervention, long term improvements in identification of happiness expressions were associated with greater ADOS severity, as was matching of emotions overall and of sadness specifically.[116] In an RCT of a theory of mind training program, children with PDD-NOS improved on most measures of emotion recognition while children with Asperger syndrome improved only in understanding of complex emotions.[121] In another RCT of a group-based social skills approach, children with Asperger syndrome were more likely to be responders compared with children with PDD-NOS (p=.03).[117]

Finally, an RCT assessing a parent training approach targeting challenging behaviors examined 21 candidate predictors and moderators of outcome scores on the Home Situations

Questionnaire (HSQ) and the Aberrant Behavior Checklist, Hyperactivity/Noncompliance (ABC-H) scale.[154, 166-168] Children received either parent training plus risperidone (n=75, mean age=7.4) or risperidone alone (n=49, mean age=7.5); thus, potential moderation of effect reflects the combination of parent training and risperidone while predictors of effects reflect the impact of risperidone with or without parent training. Investigators examined variables including parent training adherence, age, IQ, family income, maternal education level, parent stress, and child baseline ratings on measures including the Vineland and ABC. Only higher baseline scores on the HSQ (greater noncompliance) predicted greater improvement in either treatment condition (p=.007), with the lower HSQ group demonstrating less mean improvement than those with higher baseline HSQ scores. Though not significant, older children had slightly more improvement than younger children. No variables predicted ABC-H outcomes, though children with higher baseline Vineland composite and communication subscale scores had greater improvement on the ABC-H. While not a predictor, greater parent adherence to the training program was correlated with better HSQ outcomes (p=.006), but adherence did not correlate with ABC-H scores. No candidate variables were found to moderate the relationship between parent training and HSQ or ABC-H outcomes, which may suggest that parent training is appropriate for the broader range of children with ASD.

Adaptive Behavior

Studies reported mixed findings related to outcomes associated with baseline adaptive behavior. In one retrospective cohort, positive outcomes in both the early intervention and the waitlist control groups were related to higher baseline adaptive scores.[85] In an RCT comparing risperidone alone and risperidone plus parent training, treatment gains were not associated with adaptive or maladaptive behaviors.[154, 166-168]

Language/Communication

The impact of language skills and attention to objects (vs. people) were assessed in two studies. In one RCT of the More Than Words program, the treatment group showed differential effects on child communication depending on children's baseline object interest; children with lower levels of baseline object interest had greater growth in communication skills, whereas children with higher levels of object interest showed attenuated growth.[91] In another study of play-focused intervention, children with baseline expressive language abilities below 11.3 months showed greater gains in language in the intervention group vs. control (effect size=0.25 for 24 children with low language skills).[146]

An RCT evaluating an imitation-based approach to affect social functioning[142, 143]assessed whether changes in social functioning were tied to changes in participants' imitation skills. Gains in imitation were associated with the number of spontaneous play acts at baseline; however, changes in imitation were not shown to be associated with gains in social functioning. This finding could be because the study had too few participants (n=27) to detect such an effect.

Other Factors

One RCT compared the effects of a 6-week joint attention or symbolic play intervention with a control arm in participants receiving 30 hours of early intervention; at the 5 year followup, investigators assessed diagnoses and language skills for 40 of the 58 original participants.[130, 131, 138, 139]Investigators also identified potential predictors of vocabulary and cognitive changes via regression analyses. Potential predictors included child age, sex, maternal education, play levels

and types, and joint attention responses. Ability to use spoken language at followup ("passing" the language assessments) was predicted by children's average play level at baseline ($p<.01$). Number of functional play types at baseline predicted greater cognitive skills. Younger age at baseline, initiation of joint attention, play level and treatment group assignment (either joint attention or symbolic play) predicted subsequent vocabulary ability (all $p<.03$); these factors together explained 64 percent of spoken language variability. Importantly, this study is limited in that children were often receiving intensive levels of intervention outside of the intervention setting, making impact of prescribed intervention hard to determine.

Parent-Related Factors

Three early intervention studies assessed variables related to parents/caregivers. In one RCT incorporating parent training,[71, 103] parents in the additional treatment group showed increased responsiveness to their children during videotaped interactions, which was correlated with reduced autism symptom severity ($p=.049$). No between-group differences were found in adaptive behavior or parenting stress. In another parent training RCT, parents in the professionally led group with low baseline self-efficacy reported higher followup self-efficacy levels than parents in the video arm.[98] In a report[86] also including a population reported in a retrospective cohort[85], parental stress was not associated with any outcomes.

Two play/interaction-focused RCTs assessed parent responsiveness and adherence to the treatment approach on treatment effects. One study comparing an 8-week caregiver-delivered joint attention approach with a waitlist control assessed intensity of total hours of intervention (external to the study), investigator-rated quality of caregiver participation, and parent-rated adherence as predictors of outcomes at the 12-month followup.[140] Greater caregiver quality of involvement predicted increased joint engagement ($p<.05$) but not other play skills or engagement outcomes. Parent-rated adherence or competence did not predict changes in any outcome. Number of hours of other intervention similarly did not predict any outcomes.[140]

Another RCT compared a 12-week intervention targeting parental responsiveness to children's playtime communication compared with a control group that received some parental education about developmental and educational needs.[146] Investigators also explored relationships among maternal synchronization (responsiveness to child communications) and long-term (12 months post-intervention) child language outcomes. Maternal synchronization was moderated by baseline maternal insightfulness ($p<.05$) and synchronization was greater in those mothers rated as insightful compared with non-insightful (effect size=0.31, $p<.05$). The link between short-term gain in maternal synchronization and long-term language (12 months post-treatment) gains was not moderated by maternal insightfulness, nor did initial language skills moderate the link between gains in maternal synchronization after 12 weeks and long term gains in expressive language.[146]

Intervention-Related Factors

Several studies of early intensive behavioral and developmental approaches evaluated potential effects associated with intervention. In an RCT evaluating the LEAP program (full training compared with training manuals only), the students of teachers rated as having better intervention fidelity showed better outcomes on all measures.[83] In other studies assessing ABA-based early intervention, where examined, total hours of intervention per week were not associated with cognitive or adaptive outcomes, although hours were similar across intervention

groups within each study (e.g., comparing half-day programs to other half-day programs).[75-77, 80-82] In a retrospective cohort study,[85] outcomes were related to age at enrollment, treatment duration, and higher baseline adaptive scores, with duration becoming nonsignificant after accounting for group membership (correlation of duration, group=.57, $p < .01$). A significant interaction emerged between age at enrollment and group membership, with younger starting age influencing outcomes for the treatment group but not control.[85]

In one parent training RCT evaluating ESDM, total intervention hours were associated with reduced restrictive and repetitive behavior and nonsocial orienting and improved developmental quotient and vocabulary comprehension in analyses combined the intervention and usual care groups.[96] In a study comparing 1:1 home-based ABA early intervention (both university-provided and privately-provided) to community-based treatment-as-usual, IQ remained stable for children in the community-based group and significantly declined for children who received university-provided ABA intervention (effect size=.49). This result is confounded by nonrandom assignment and the fact that at baseline, the university-based group had higher levels of autism symptoms, lower levels of adaptive behavior, and fewer total intervention hours.[78, 79] Finally, in a prospective cohort study, hours of intervention did not correlate with outcomes.[76]

KQ3. Treatment Phase Changes That Predict Outcomes

No studies were identified that provided data on changes early in treatment that predicted outcomes.

KQ4. Treatment Effects That Predict Long-Term Outcomes

Few studies assess end-of-treatment effects that may predict long-term outcomes. Several early intensive behavioral and developmental interventions change measures over the course of very lengthy treatments, but such outcomes usually have not been assessed beyond treatment windows. One family of studies[130, 131, 138, 139] attempted to follow young children receiving early joint attention intervention until they were school aged, but this failed to include adequate followup of the control group. It also involved children who were receiving many hours of uncontrolled interventions during the course of study.

KQ5. Generalization of Treatment Effects

Few studies measured generalization of effects seen in treatment conditions to either different conditions or different locations; however, several studies incorporated parent- or teacher-delivered components, which may promote generalization of skills to the home and classroom.

Among play/interaction-focused studies, one study of imitation training reported that gains in elicited imitation skills in the treatment group were also reflected in improvements in motor imitation skills, suggesting transfer of skills learned in the intervention.[142, 143] In a prospective cohort study assessing an intervention targeting pretend play, treatment group participants maintained their level of play dialog with novel toys when scripted dialog (a component of the initial intervention) was not provided.[148] Three interventions targeting joint attention skills based in preschools reported generalization: in one, increases in joint attention initiations with preschool teachers generalized to longer duration of joint engagement with mothers (10% increase from baseline compared with 2% decrease for control group).[145] Time jointly engaged with preschool teachers, however, did not increase. Two other studies[141, 147] suggested that joint

attention skills training transferred to the classroom with treatment group participants spending less unengaged time and/or initiating more gestures.

Studies of early intervention approaches reported greater socially engaged imitation that generalized across settings and context in the treatment group,[101, 102] increased frequency of joint attention acts with an unfamiliar examiner,[91] and maintenance of skills over time and in the home and center-based setting.[99, 100] One study of a social skills intervention reported increases in participant social skills on intervention staff-rated but not parent-rated measures for either a Skillstreaming group or comparison group receiving a sociodramatic relational intervention.[122] In another social skills study, parents of children in a program enhanced for children with high functioning ASD reported improvements in their children's skills in various settings while parents of children in a traditional social skills group did not.[119] Finally, an analysis of Vineland and parental intrusiveness scores across income categories revealed no significant differences in one study of CBT, suggesting that the intervention is applicable across income levels.[153, 165, 178]

KQ6. Treatment Components That Drive Outcomes

We did not identify any studies meeting our inclusion criteria and addressing this 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. In our 2011 review we identified two comparative studies (one good quality RCT[72] and one fair quality nonrandomized clinical trial[73]) addressing interventions for very young children. For the current review, we identified three studies[91, 95, 97] addressing treatment approaches for very young children. One crossover RCT was conducted in China (poor quality),[97] one prospective cohort study in Europe (poor quality),[95] and one RCT in the United States (fair quality).[91]

The mean age in most studies exceeded 24 months, although one[91] included children under age two. Mean ages were all under three years, and all studies address interventions that can be used with children under age 2. The average age for diagnosis of ASD in the United States is not until at least age 3, but a reliable diagnosis may be possible as early as age 2.

One fair quality RCT was completed in the clinic and home settings.[91] The two poor quality studies, one crossover RCT and one prospective cohort study,[95, 97] included groups receiving in-home parent training.

The fair quality RCT focused on enhancing parental responsivity and child communication.[91] It compared Hanen's More Than Words intervention to treatment-as-usual. The treatment group (n=29, mean age=21.11 ± 2.71 months) received eight manualized group sessions with parents only and three in-home individualized parent-child sessions over a span of 3.5 months, whereas the control group (n=26, mean age=21.61 ± 2.82 months) received no treatment or treatment as usual. There was no treatment effect on parental responsivity. The treatment group showed differential improvement on child communication depending on children's baseline object interest; children with lower levels of baseline object interest had greater growth in communication skills, whereas children with higher levels of object interest showed attenuated growth. Two poor quality studies compared parent training to lower intensity supportive interventions. Mean ages ranged from 25.33-33.6 months. Both involved home visits and

working with children and parents. The lower intensity treatment model, Autism-1-2-3, compared two groups that received the same series of ten thirty-minute child- and parent-training sessions, with one group having a lagged start date and serving as a control. It did not yield group differences on autism symptoms, language skills, or parent stress scores.[97] The higher intensity model, Keyhole, incorporated elements of Hanen's More than Words and the TEACCH programs.[95] It compared 15-18 home visits over a 9 month period (n=35) targeting adaptive skills, autism symptoms, and parent stress to a lower-intensity intervention model (n=26; 5 home visits, no additional services of supports). Compared with the control group, children in the treatment group showed improved adaptive, imitation, and communication skills, based only upon parent report. Mothers in the treatment group also reported improved health but did not report decreases in parenting stress.

In summary, young children who received behavioral interventions seemed to improve regardless of intervention type. It is important to note that none of the fair or better quality studies of young children compared children getting treatment to a no treatment control group. One poor quality study reported positive effects of treatment,[95] but the level of intervention intensity varied significantly between groups, and it is unclear whether the effects were due to intensity versus the treatment type. Potential modifiers of treatment efficacy include baseline levels of object interest.[91] Most outcome measures of adaptive functioning were based upon parent report, and the effect of parental perception of treatment efficacy on perception of child functioning was generally not explored.

Discussion

In this chapter, we summarize our findings about behavioral interventions for children with autism spectrum disorder (ASD). We provide an overview of the state of the literature by intervention type, detail the strength of evidence for the impact of each major intervention on relevant outcomes, and describe major issues and gaps in the current body of evidence.

Assessing the literature requires consideration of two main components, namely the observed effectiveness of interventions and our confidence that those effects will remain stable in the face of future research. Our confidence that the observed effect is the true effect and that perceived effectiveness is unlikely to change with future research is presented as strength of evidence, and can be insufficient, low, moderate or high. Strength of evidence describes the adequacy of the current research, both quantity and quality, and whether the entire body of current research provides a consistent and precise estimate of effect. Interventions that demonstrate significant benefit in a small number of studies but have not yet been replicated using rigorous study designs will have insufficient or low strength of evidence, despite potentially offering clinically important benefits.

Methods for applying strength of evidence assessments are established in the Evidence-based Practice Centers' *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[54] and are based on consideration of five domains: study limitations, consistency in direction of the effect, directness in measuring intended outcomes, precision of effect, and reporting bias. We required at least three fair studies to be available to assign a low strength of evidence rather than considering it to be insufficient. We required at least one good study for moderate strength of evidence and two good studies for high strength of evidence. In addition, to be considered "moderate" or higher, intervention-outcome pairs needed a positive response on two out of the three domains other than risk of bias.

Once we established the maximum strength of evidence possible based upon these criteria, we assessed the number of studies and range of study designs for a given intervention-outcome pair, and downgraded the strength of evidence rating when the cumulative evidence was not sufficient to justify the higher rating.

Key Findings and Strength of Evidence

KQ1. Effects of Behavioral Interventions on Core and Commonly Associated Symptoms in Children With ASD

Early Intensive Behavioral and Developmental Interventions

Within this category, we included intensive behavioral and developmental interventions derived from applied behavior analysis (ABA) principles that targeted a broad range of skills and vulnerabilities. As such, this category includes defined manualized approaches that vary substantially in terms of their structure, approach and setting (e.g., University of California, Los Angeles [UCLA]/Lovaas, Early Start Denver Model [ESDM], Learning Experiences and Alternate Program for Preschoolers and their Parents [LEAP]) as well as more eclectically defined and delivered approaches. ABA is an umbrella term describing principles and techniques used in the assessment, treatment and prevention of challenging behaviors and the promotion of new desired 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.

An additional set of interventions included here uses the principles of ABA to focus on key pivotal behaviors rather than global improvements. These approaches emphasize parent training (e.g., Pivotal Response Training, Hanen More than Words, social pragmatic intervention, etc.) and may focus on core social-communication skills or specific behaviors, such as initiating activities.

We located 31 papers comprising 21 unique studies addressing early intensive behavioral and developmental interventions. Individual studies using intensive UCLA/Lovaas-based interventions, ESDM, the LEAP program, and eclectic variants reported improvements in outcomes for young children. Improvements were most often seen in cognitive abilities and language acquisition with less robust and consistent improvements seen in adaptive skills, core ASD symptom severity, and social functioning.

Young children receiving high intensity ABA-based interventions over the course of extended time frames (i.e., 8 months--2 years) commonly display substantial improvement in cognitive functioning and language skills relative to community controls. However, the magnitude of these effects varies across studies and this variation may describe subgroups showing different responses to particular interventions. Intervention response is likely moderated by both treatment and child factors, but exactly how these moderators function is not entirely clear . Despite multiple studies of early intensive treatments, intervention approaches still vary substantially, which makes it difficult to tease apart what these unique treatment and child factors may be. Further, the long-term impact of these early skill improvements is not yet clear, and many studies did not follow children beyond late preschool or early school years.

Studies of high intensity early intervention services also demonstrated improvements in children's early adaptive behavior skills, but these improvements are more variable than those found for early cognitive and language skills. Treatment effects are not consistently maintained across studies. Many studies measure different adaptive behavior domains (which creates within scale variability) and some evidence suggests that adaptive behavior changes may be contingent upon baseline child characteristics, such as cognitive/language and autism severity.

Evidence for the impact of early intensive intervention on core ASD symptoms is more limited and mixed than its impact on cognitive and adaptive behavior skills. Children's symptom severity often decreased during treatment, but these improvements did not often differ from those of children in control groups. In fact, almost equal numbers of studies report treatment impact versus null treatment effects.

Since our previous review, there have been substantially more studies of well-controlled low intensity interventions that provide parent training in bolstering social communication skills. This growing literature base provides increasing evidence about the utility of such interventions for younger children with ASD, particularly when targeting social communication and language use. However, although parent training programs certainly modified parenting behaviors during interactions, data are more limited about their ability to improve broad developmental skills (such as cognition, adaptive behavior, and ASD symptom severity) beyond language gains for some children. Children receiving low-intensity interventions have not demonstrated the same substantial gains as seen in the early intensive intervention paradigms regarding cognitive and adaptive skills.

Strength of the Evidence

A growing evidence base suggests that children receiving early intensive behavioral and developmental interventions (e.g., many hours of intervention a week over the course of 1-2 years) show substantial improvements in cognitive and language skills over time compared with children receiving low-intensity interventions, community controls, and eclectic non-ABA based intervention approaches. With this growing literature, our confidence (strength of evidence) in the effects of ABA-based early intensive approaches on cognitive and language outcomes is moderate, based on the need for additional research that identifies which groups of children benefit the most from specific high intensity approaches. Our strength of evidence in these high intensity interventions to affect adaptive behavior skills, social skills, and core ASD symptom severity is low. At present it is challenging to understand which high intensity variants most robustly impact these domains for specific children and in general the impact of these skill domains is less consistent (Table 12).

The evidence base for parent training interventions is moderate for their impact on early language and communication skills and low for impact on ASD symptom severity and early cognition. There is not yet sufficient data from this literature base to understand impact on adaptive behavior skills. Available studies indicate variable responses, with modest improvement for some children in some approaches, but limited improvement in other parent training paradigms (Table 13).

Table 12. Strength of Evidence for ABA-based Early Intensive Behavioral and Developmental Studies

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
IQ/cognitive **Moderate**	RCT: 1 good, 2 fair (360) Prospective cohort: 6 fair, 2 poor (521) nRCT; 4 fair (130) Retrospective cohort: 1 fair, 2 poor (182)	Medium	Consistent	Direct	Precise	Undetected	Young children receiving high intensity interventions display improvements in aspects of cognitive functioning. Most studies found that children in treatment and comparison groups both improved on cognitive skills, with children in high intensity early intensive intervention improving more than children receiving other types of services. Not all of these improvements were maintained at long-term followups. Many children display a positive response to this intervention, but the effect is somewhat variable across studies and may be indicative of subgroups with variable response. Across studies where positive effects were seen, the actual treatment impact on skills may vary based on child and intervention factors. A key limitation is that although there are many more studies of early intensive formats, approaches across studies still vary substantially, and it is hard to determine the effects of these unique studies on specific groups of children.

Table 12. Strength of Evidence for ABA-based Early Intensive Behavioral and Developmental Studies, continued

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
Adaptive behavior **Low**	RCT: 1 good, 1 fair (76) Prospective cohort: 7 fair, 2 poor (616) nRCT: 4 fair (130) Retrospective cohort: 1 fair, 2 poor (182)	Medium	Inconsistent	Direct	Imprecise	Undetected	Most studies found that children in both treatment and control groups improved on adaptive skills. However, children in high intensity early intensive intervention improved more than children receiving other types of services. Not all group differences were maintained over long-term followup. There was variability within domains, such that some studies found improvement whereas others found declines in domain standard scores. For example, one study found a decrease in the motor skills domain for both treatment and control groups. An important limitation is that adaptive behavior was always measured by parent report (Vineland) rather than objective observation. Some studies suggested that adaptive behavior outcomes were dependent on baseline child characteristics, such as cognitive and verbal abilities and autism severity.

Table 12. Strength of Evidence for ABA-based Early Intensive Behavioral and Developmental Studies, continued

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
Symptom severity **Low**	RCT: 1 good, 1 fair (332) nRCT: 1 fair (34) Prospective cohort: 4 fair, 2 poor (470) Retrospective cohort: 1 fair (142)	Medium	Inconsistent	Direct	Imprecise	Undetected	The impact of early intervention on symptom severity was mixed, with approximately equal numbers of studies finding and not finding treatment effects. Most control groups were also receiving treatment and also showed improvement, making it difficult to tease apart the effect of early intensive intervention specifically vs. any kind of intervention. Evidence emerged that baseline symptom severity predicts response to treatment, although the direction is inconsistent
Language/ commun-ication **Moderate**	RCT: 1 good, 2 fair (360) nRCT: 3 fair (103) Prospective cohort: 6 fair, 2 poor (616)	Medium	Consistent	Direct	Precise	Undetected	Most studies found a positive effect of treatment on language/communication skills, although the specific domain of improvement (e.g., receptive vs. expressive language) varied across study Some initial between-group differences disappeared at long-term followup. Some evidence that baseline child factors such as gender and cognitive skills influenced effects of treatment on language outcomes A limitation is that some studies measured language using direct testing, whereas others only used the Vineland Communication domain

Table 12. Strength of Evidence for ABA-based Early Intensive Behavioral and Developmental Studies, continued

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
Social skills/social behavior **Low**	RCT: 1 good, 1 fair (332) nRCT: 1 fair (34) Prospective cohort: 4 fair, 1 poor (406) Retrospective cohort: 1 fair (142)	Medium	Inconsistent	Direct	Imprecise	Undetected	Many studies found that treatment groups improved more than controls on measures of social skills, although a significant minority did not find any treatment effect. A significant limitation is that social skills were assessed almost exclusively using parent-reported standard scores on the Vineland.

ABA-applied behavior analysis; nRCT-nonrandomized controlled trial; RCT-randomized controlled trial

Table 13. Strength of the evidence for early intervention-parent training studies

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
IQ/cognitive **Low**	RCT: 1 good, 3 fair (232) Prospective cohort: 1 good, 1 fair (110)	Medium	Inconsistent	Direct	Imprecise	Undetected	Few early intervention-parent training studies examined cognitive skills. Of those that did, two found that treatment groups improved more than controls and two found no treatment effects.

Table 13. Strength of the evidence for early intervention-parent training studies, continued

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
Symptom severity **Low**	RCT: 3 good, 3 fair (361) Prospective cohort: 1 good, 1 fair, 1 poor, (171)	Low	Inconsistent	Direct	Imprecise	Undetected	Many studies found that treatment groups had improved autism symptoms relative to controls. However, a significant limitation is that the measure of symptom severity varied across studies and was inconsistently defined, from videotaped behavioral observations to standardized parent report forms like the GARS to interactive assessments like the ADOS. This makes it difficult to meaningfully compare outcomes across studies.
Language/ commun-ication **Moderate**	RCT: 3 good, 5 fair, 1 poor (574) nRCT: 1 poor (22) Prospective cohort: 2 good, 1 poor (144)	Low	Consistent	Direct	Precise	Undetected	Some studies found differential impacts of treatment type on language comprehension vs. expression, although results were mixed, with many studies not finding treatment effects. Of studies that assessed language outcomes, two possible child variables influencing treatment efficacy emerged. The first is that younger child age was associated with greater language improvements at followup in two studies. Second, another study found that higher baseline levels of object interest in children were associated with attenuated growth in communication skills.

ADOS-Autism Diagnostic Observation Schedule; GARS-Gilliam Autism Rating Scale; nRCT-nonrandomized controlled trial; RCT-randomized controlled trial

Social Skills Studies

We located 10 studies addressing interventions targeting social skills. The overall quality of studies improved compared with the previous review with two good quality and eight fair quality studies. Social skills interventions varied widely in terms of scope and intensity. A few studies replicated interventions using the manualized Skillstreaming model; other studies incorporated peer-mediated and/or group-based approaches, and still others described interventions that focused on emotion identification and theory of mind training. The studies also varied in intensity, with most interventions consisting of 1-2 hour sessions/week lasting for approximately 4-5 weeks. However, some of the group-based approaches lasted for 15-16 weeks.

Most studies reported some short term gains in either parent-rated social skills or directly tested emotion recognition. However, our confidence (strength of evidence) in that effect is low. While we now have higher quality investigations of social skills interventions demonstrating positive effects, our ability to determine the effectiveness of these interventions continues to be limited by the diversity of the intervention protocols and measurement tools (i.e., no consistent outcome measures used across studies). Maintenance and generalization of these skills beyond the intervention setting is also inconsistent, with parent- and clinician-raters noting variability in performance across settings. No studies reported harms of intervention.

Strength of the Evidence

The strength of evidence for the effect of social skills interventions on social outcomes for school aged children with ASD is low. All studies demonstrated benefit on at least one outcome measure, but a lack of consistency in the interventions or measures used makes it difficult to assess consistency or precision. Most studies relied on parent or teacher report of intermediate outcomes, although some studies have attempted to included ratings and outcomes (peer/teacher nominations, social networks/maps) with potential for assessment of generalization (Table 14).

Table 14. Strength of the evidence for social skills studies

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
Social skills/social behavior **Low**	RCT: 2 good, 10 fair, 5 poor (696) nRCT: 1 fair (21) Retrospective cohort: 1 poor (117)	Medium	Inconsistent	Direct	Precise	Undetected	School-aged children diagnosed without concomitant cognitive and language deficits demonstrated short-term gains in social skills and emotion recognition. Maintenance and generalization of these skills beyond the treatment context had variable results. Social skills interventions varied widely in terms of scope and intensity.

nRCT-nonrandmized controlled trial; RCT-randomized controlled trial

Play- /Interaction-Focused Studies

Studies incorporating play or interaction-based elements have targeted either joint attention skills, early imitation skills, or focused play in younger children. No studies reported harms of intervention.

Since our previous review, there have been substantially more studies of well-controlled joint attention interventions across a range of intervention settings (e.g., clinician, parent, teacher delivered). Regarding joint attention skills, interventions were delivered by parents, teachers, and interventionists over typically short durations (≤ 12 weeks). Three studies reported longer-term followup (≥12 months).[130, 131, 138-140, 146] As with other studies reported in this review, participants in play/interaction studies often received other early intervention services in addition to the targeted intervention, making disentangling effects of the intervention difficult.

This growing evidence base supports positive effects for young and preschool children with ASD, particularly when targeting joint attention skills themselves as well as related social communication and language skills. Although joint attention intervention studies certainly demonstrated changes within this theoretically important domain, data are more limited about their ability to improve broad developmental skills (such as cognition, adaptive behavior, and ASD symptom severity) beyond communication and language gains over time.

Specific and focal training regarding imitation skills utilizing naturalistic approaches to promote imitation (i.e., Reciprocal Imitation Training) has shown positive results in improving not only imitation skills, but potentially other social communication skills such as joint attention as well.[142, 143] Additionally, parent training in a variety of play-based interventions is associated with positive outcomes for encouraging early social communication skills (e.g., joint attention, engagement, play interactions), play skills, and early language skills.[144, 146]

Strength of the Evidence

A growing evidence base suggests that children receiving early joint attention-related intervention in combination with other interventions show substantial improvements in joint attention and language skills over time. Within this growing literature, our confidence (strength of evidence) in this effect is moderate, based on the need for additional research that identifies which groups of children benefit the most from this approach and how this intervention relates to other ongoing concurrent offered interventions. Results from a variety of play-based interventions also suggest that young children often display short-term improvements in early play, imitation, language, and social interaction skills. However, our confidence in these estimates is low, and substantial evidence that these short-term improvements are linked to broader indices of change over time is lacking (Table 15).

Table 15. Strength of the evidence for play/interaction-based studies

Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
Joint attention **Moderate**	RCT: 3 good, 3 fair (213)	Low	Consistent	Direct	Precise	Undetected	Selected joint attention skills consistently increased in treatment arms, but duration of effects is unclear
Play skills **Low**	RCT: 3 good, 1 fair, 3 poor (196) Prospective cohort: 1 poor (12)	Medium	Consistent	Direct	Precise	Undetected	Play skills increased in treatment arms but duration of effects is unclear Imitation skills improved in treatment arms in 4 small, short-term studies
Language/ Communication **Low**	RCT: 3 fair (142)	Medium	Consistent	Direct	Imprecise	Undetected	Expressive but not receptive language skills generally increased in the treatment arms in 2 studies; prompted but not spontaneous communication improved in 1 study
Social skills **Low**	RCT: 1 good, 3 fair (173)	Medium	Consistent	Indirect	Precise	Undetected	Joint engagement or positive affect improved in treatment arms in 3 studies

RCT-randomized controlled trial

Interventions Targeting Conditions Commonly Associated With ASD

Most studies in this category evaluated the impact of cognitive behavioral therapy (CBT) on co-occurring conditions, such as problem behaviors or anxiety, rather than core autism symptoms or broader developmental domains (e.g., cognition, language, adaptive behavior). Five of six RCTs identified in the literature measured anxiety symptoms as a primary outcome. Four of these studies reported significantly greater improvements in anxiety symptoms in the intervention group compared with controls. Two of these studies found positive effects of CBT on the core autism symptom of socialization. The one RCT that did not find a significant benefit of CBT compared it to social recreational therapy rather than treatment as usual or a waitlisted control group. Although the CBT group had improved anxiety symptoms, this improvement did not significantly differ from participants receiving social recreational therapy.[161]

The studies examining the effects of CBT on anxiety had largely consistent methodologies and primarily conducted weekly 60-90 minute treatment sessions over a period of 4 months. All studies provided followup data reflecting treatment effects that lasted beyond the period of direct intervention. Two common factors limit the applicability of the results, however. Due to the nature of CBT, which is often language-intensive and requires a certain level of reasoning skills to make abstract connections between concepts, most studies included only children with IQs much greater than 70. This likely restricts the applicability of findings to the general population of people with ASD. Additionally, the CBT interventions described in these studies included both children and parents, suggesting that both components may be necessary for effective treatment.

These studies are encouraging regarding the use of CBT to treat anxiety in children with ASD. They also suggest that CBT could potentially be associated with improvements in socialization and communication, although these results were less robust and it is unclear if these improvements were beyond improvements related to the impact of ameliorated anxiety itself.

Additional data in the current review relate to parent training to address challenging behavior. Specifically, one good quality study combined a parent training approach with risperidone. This combination significantly reduced irritability, stereotypic behaviors, and hyperactivity, and improved socialization and communication skills. However, these effects were not maintained at one-year post-treatment. The followup sample size also decreased from 124 to 87.[154, 166-168]

Strength of the Evidence

A growing evidence base suggests that school-aged children with average to above average intelligence and comorbid anxiety symptoms receiving manualized CBT therapy show substantial improvements in anxiety compared with wait-list controls. Within this population our confidence (strength of evidence) in this effect is high. Our strength of evidence of the impact of this intervention for this same group on ASD symptoms (social communication functioning and repetitive behaviors) is low with future research likely affecting our understanding of the unique impact of this intervention. With regard to parent training paradigms to address challenging behavior, results of parent training studies and parent training in addition to treatment with risperidone have demonstrated short-term improvements in terms of the frequency and intensity of challenging behavior. Our confidence in this effect is low (Table 16).

Table 16. Strength of the evidence for studies addressing interventions targeting commonly associated conditions

Intervention/ Outcome Strength of Evidence Grade	Study Design Quality and Number of Studies (N Total Participants)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding
CBT							
Anxiety **High**	RCT: 6 good, 2 poor (401) nRCT: 1 fair (31)	Low	Consistent	Direct	Precise	Undetected	Most studies included older children with average IQs. Improvement in anxiety symptoms for greater for CBT vs. control group in 5/6 studies. The study that did not show improvement compared CBT to an active treatment instead of a waitlisted control. Improvement was maintained at followup. Some evidence emerged that CBT may be more effective for some types of anxiety disorders than others.
Symptom severity **Low**	RCT: 2 good (81)	Low	Consistent	Direct	Precise	Undetected	Improvement in severity of symptoms had large effect in both studies. Improvement was maintained at followup.
Parent Training							
Challenging behavior **Low**	RCT: 1 fair, 1 poor (146) Prospective cohort: 1 poor (106)	Medium	Consistent	Direct	Imprecise	Undetected	Improvement in challenging behavior was demonstrated in both studies examining effects of parent training. In the study that performed one year followup, differences in improvement were lost. However the sample size was significantly smaller. An important limitation is that measures of challenging behavior in the good-quality study were all based on parent report.

CBT-cognitive behavioral therapy; nRCT-nonrandomized controlled trial; RCT-randomized controlled trial

Other Behavioral Studies

Two studies examined neurofeedback and found some improvements on parent-rated measures of communication and tests of executive function. The clinical implications of changes in brainwave patterns reported in the studies is unclear, and the studies were small and short-term.[174, 176, 177] Two studies reported on sleep-focused interventions, with little positive effect of a sleep education pamphlet for parents in one[172] and improvements in sleep quality in treatment arms (melatonin alone, melatonin+CBT) in another.[173]

Strength of the Evidence

With few studies of additional behavioral interventions, all of limited quality, there is insufficient evidence to evaluate the relative effect of other behavioral interventions on targeted outcomes including ASD symptom severity, problem behaviors, and sleep concerns. Table 17 outlines interventions/outcomes for which we considered the strength of the evidence to be insufficient.

Table 17. Behavioral interventions/outcomes with insufficient strength of evidence by outcomes assessed

Intervention	Anger	Adaptive behavior	Symptom severity	Repetitive behavior	Language/communication	Challenging behavior	Sleep parameters	Social skills	Executive function
CBT (commonly associated conditions)	✓	✓							
Parent training (commonly associated conditions)		✓	✓						
Social skills			✓	✓	✓				
Play/interaction-based interventions						✓			
CBT(other behavioral interventions)							✓		
Sleep education pamphlet (other behavioral interventions)							✓		
Neurofeedback (other behavioral interventions)					✓			✓	✓

CBT-cognitive behavioral therapy

KQ2. Modifiers of Treatment Effects

Understanding the degree to which child characteristics (i.e., specific ASD-related difficulties and skills), treatment factors (e.g., type, duration, intensity), and systems (e.g., family, community) influence response to intervention could help professionals target treatments to the appropriate children and circumstances. However, as was reported in the 2011 review, few studies were clearly designed or powered to allow for analysis of heterogeneous effects. Primarily studies in this section are those in which potential correlates were identified that may

be moderators, but have not been studied as such. These potential moderators should be assessed in properly designed and powered studies for this purpose.

Among early intensive ABA-based interventions potential modifiers or moderators, younger age at intake was generally associated with better outcomes for children; however, this finding was not present in some other studies.[116, 154, 166-168] Higher cognitive skills and higher adaptive behavior scores at baseline were also often associated with better outcomes across behavioral interventions, but the associations were not consistent. In general, children with lower symptom severity or less severe diagnoses improved more than participants with greater impairments. However, many studies (e.g., those of social skills, CBT) often restricted the range of participants' impairment at baseline, limiting understanding of intervention impact on broader populations. Studies assessing parental responsiveness to children's communication typically reported better outcomes in children whose parents were more aligned with the child's communication versus those who attempted to re-direct or were less synchronized with it. Regarding intervention-related factors, duration of treatment had an inconsistent effect, with some studies reporting improved outcomes with greater intervention time and others reporting no association. Studies have often not been adequately designed or controlled in order to help identify true moderators of treatment. More often post-hoc evaluation of differences across groups has been examined.

KQ3. Treatment Phase Changes That Predict Outcomes

Information about early response to treatment (or lack thereof) could guide treatment selection, implementation, and modification. The reviewed literature offers little information about what specific early changes from baseline measurements of child characteristics might predict long-term outcome and response. Some evidence suggests that the best predictor of long-term outcome is not baseline characteristics at all, but rather the magnitude of change seen over the course of treatment (e.g., cognitive shifts in first years of early intensive treatments).[72, 84]

KQ4. Treatment Effects That Predict Long-Term Outcomes

Few studies assess end-of-treatment effects that may predict outcomes. Several early intensive behavioral and developmental intervention paradigms change measures over the course of very lengthy treatments, but such outcomes usually have not been assessed beyond treatment windows. One family of studies[130, 131, 138, 139] attempted to follow young children receiving early joint attention intervention until they were school aged, but this study failed to include adequate followup of control conditions. It also involved children were receiving many hours of uncontrolled interventions during the course of study.

KQ5. Generalization of Treatment Effects

Few studies included in this review explicitly measured generalization of treatment effects to different conditions or locations. Often, early intensive behavioral and developmental interventions attempted to index change by examining standardized cognitive skills, adaptive behavior, and language measures in addition to metrics of ASD symptoms. Presumably, changes measured on these instruments document important skills with potential impact in other areas. However, some caution is warranted: In some instances, the interventions themselves may actually target component skills of these assessments, particularly in the case of cognitive and language assessments.

The majority of the social skills and behavioral intervention studies targeting associated conditions attempted to index outcomes based on parent, self, teacher, and peer report of targeted symptoms (e.g., anxiety, externalizing behaviors, social skills, peer relations) at home, at school, and in the community. While such ratings outside of the clinical setting may be suggestive of generalization in that they improve outcomes in the daily context/life of the child, in most cases, these outcomes are parent reported and not confirmed with direct observation. Behavioral intervention studies rarely measured outcomes beyond the intervention period, and therefore we cannot assume that effects are maintained over time.

KQ6. Treatment Components That Drive Outcomes

We again did not identify any studies meeting our inclusion criteria that addressed this question.

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

In the studies addressing interventions for younger children,[91, 95, 97] children who received behavioral interventions seemed to improve regardless of intervention type. None of the fair or good quality studies compared treatment groups to a no treatment control group. One poor quality study found positive differential effects of treatment,[95] but the level of intervention intensity varied significantly between groups, making it difficult to differentiate the effects of treatment intensity vs. type. Potential modifiers of treatment efficacy include baseline levels of object interest.[91] Most outcome measures of adaptive functioning were based upon parent report, and the effect of parental perception of treatment efficacy on perception (and report) of child functioning was generally not explored.

Findings in Relation to What is Already Known

Other reviewers have also synthesized the impact of early intensive behavioral interventions. We rated three meta-analyses evaluating early intervention for children with ASD that were published since the 2011 review as good quality.[45, 52, 179] We also summarize two overview meta-analyses (not quality rated) addressing early intervention.[180, 181] Findings of other reviews assessing effects of early intensive ABA-based intervention largely align with our evaluation of the strength of evidence. Specifically, other reviews have demonstrated consistent impact on cognitive and language skills with fairly large effect sizes across these somewhat overlapping syntheses. These same investigations have also noted much less consistent changes in adaptive behavior skills. Further, these reviews have highlighted similar methodological concerns as noted in our current review: relatively small sample sizes, inclusion of nonrandomized studies, lack of standardized control groups, errors in interpretation of studies, and wide variations in the early intervention approaches assessed.

One Cochrane review compared early intervention to treatment as usual and included RCTs or controlled trials with participants under 6 years of age at intake.[45] The review included 5 studies (one RCT) with a total of 203 participants (mean age range: 30.2 to 42.5 months). The investigators rated all studies as having high risk of bias (low overall quality) and found positive effects for early intervention on all outcomes. Mean difference effect sizes were 0.76 for IQ (95% CI=0.40 to 1.11, p<.0001), 0.69 for adaptive behavior (95% CI=0.38 to 1.01, p<.0001) and ranged from 0.42 to 0.74 for measures of communication, socialization, and daily living skills (p

values .0005 to .03). Tests of heterogeneity and small sample sizes precluded assessment of moderators of effects.

One meta-analysis of ABA-based interventions included studies with at least five children with ASD receiving at least 10 hours of intervention per week for 45 weeks. Twenty-two studies met criteria and assessed outcomes including IQ, receptive and expressive language, and adaptive behavior (Vineland composite and subscales). Studies included 323 patients (mean age 22.6 to 66.3 months, 55.6 to 97% male). Study quality was low to moderate, ranging from 1.2 to 3.6 on a five point scale (mean 2.5). Thirteen studies had control groups (six with random/quasi-random assignment). Positive effects were associated with ABA-based intervention in 18 studies assessing the outcome with a pooled effect size of 1.19 (95% CI: 0.91 to 1.47, p<.001). Similarly, ABA was associated with positive effects on language (general, expressive, and receptive, effect sizes from 1.07 to 1.48) and adaptive behavior (communication, socialization, motor skills, daily living skills domains as well as composite scores; pooled effect sizes ranging from 0.61 to 1.45). The effect size for the composite score was 1.09 (95% CI: 0.70 to 1.47, p<.001), and total treatment duration was associated with better adaptive behavior and language outcomes but not IQ. Results restricted to studies with control groups were consistent with results for all studies across outcomes. Across outcomes, effect sizes were generally slightly better for clinic-based approaches vs. parent-delivered. Similarly, the investigators note the potential for publication bias for the outcomes of IQ and language and the adaptive behavior domains of communication and socialization.[52]

Another meta-analysis of ABA-based early intervention included 11 small comparative studies (one RCT) with 344 children with ASD (mean age 33.56 to 65.68 months, 65.7% male).[179] The mean quality of studies as rated on the Downs and Black scale was 24.65 out of 32 (range 23-27). The early intervention group had greater gains on all variables assessed compared with control group participants, with full scale IQ improving by 11.98 points over improvements in the control group. Receptive and expressive language scores for the early intervention group compared with control each improved by more than 13 points, while improvements on Vineland subscales scores ranged from 4.96 to 10.44 points. Total effect sizes for daily living skills improvements were moderate (0.68) and were large for improvements in IQ, language, and adaptive behavior (effect sizes ranging from 0.91 to 2.00). The authors noted some evidence of publication bias. Table 18 outlines key characteristics of these early intervention meta-analyses.

A sequential or cumulative meta-analysis compiled data from 15 studies rated as adequate or high quality in five previously published meta-analyses (Eldevik 2009, Makrygianni 2010, Peters-Scheffer 2011, Reichow 2009, Spreckley 2009).[180] The 15 studies included 263 children with ASD. The sequential meta-analysis found a medium treatment benefit for early intervention vs. comparison interventions for the outcomes of intellectual functioning, language, and adaptive behavior. The magnitude of treatment benefit varied for outcomes when assessing pre- to post-differences in the early intervention group. For IQ, the standardized mean difference effect size for group differences was 0.61 (p<.001) and the pre to post differences in the early intervention group was 0.71 (p<.01). Between group effect sizes for adaptive behavior and language were also considered medium (0.60 and 0.72, respectively, p values <.001). Pre to post effect sizes were for adaptive behavior (0.35, p=ns) and language (0.69, p<.05) did not reach sufficiency and could not be considered as providing evidence of medium pre to post treatment benefit. The authors note that meta-analyses for pre to post differences in adaptive behavior and language were underpowered.

An overview of four of the same meta-analyses noted above plus an one additional (Virues-Ortega 2010) described methodologic limitations across the meta-analyses.[181] Limitations included small sample sizes in included studies, inclusion of nonrandomized studies, lack of standardized control groups, errors in interpretation of studies, and variations in the early intervention approaches assessed. Four of the five meta-analyses concluded that early intervention was an effective approach. For IQ, the weighted mean effect size across meta-analyses ranged from 0.38 to 1.19 and from 0.30 to 1.09 for adaptive behavior. Despite the need for additional research, particularly in understanding effective treatment component and child characteristics associated with optimal outcomes, the authors conclude that early intervention can produce significant effects on IQ and adaptive behavior for many young children with ASD.

Table 18. Summary of meta-analyses of early intervention approaches

Author, Year	Study Type As Defined In Review (N) Total Participants/Group (N)	Mean Participant Age (Months)	Treatment Intensity, Hours/Week Treatment Duration, Mean Months (Range)	Effect Sizes (95% CI)
Reichow 2012[45]	RCT: 1 Controlled trial: 4 Early intervention: 116 Comparison: 87	30.2-42.5	>24 hours/week 26.3 months (14-36)	IQ: 0.76 (0.40 to 1.11) Expressive language: 0.50 (0.05 to 0.95) Receptive language: 0.57 (0.20 to 0.94) Vineland adaptive behavior: 0.69 (0.38 to 1.01) Vineland communication: 0.74 (0.30 to 1.18) Vineland socialization: 0.42 (0.11 to 0.73) Vineland daily living: 0.55 (0.24 to 0.87)
Virues-Ortega 2010[52]	Total studies (type not defined): 22 Early intervention: 323 Comparison: 180	22.6-66.3	12-45 hours/week 4-34 months	IQ: 1.19 (0.91 to 1.47) Expressive language: 1.47 (0.85 to 2.08) Receptive language: 1.48 (0.96 to 1.97) General language: 1.07 (0.34 to 1.79) Vineland adaptive behavior: 1.09 (0.70 to 1.47) Vineland socialization: 0.95 (0.53 to 1.37) Vineland communication: 1.45 (1.02 to 1.88) Vineland daily living: 0.62 (0.30 to 0.93) Vineland motor skills: 0.71 (0.19 to 1.22)
Peters-Scheffer 2011[179]	RCT: 1 Pre-test/post-test with control: 10 Early intervention: 168 Comparison: 144	33.65-65.68	12.5-38.6 hours/week 10-24+ months	IQ: 2.00 Non-verbal IQ: 0.98 Expressive language: 1.10 Receptive language: 2.91 Vineland adaptive behavior: 0.91 Vineland communication: 1.32 Vineland daily living: 0.68 Vineland socialization: 1.49

CI-confidence interval; IQ-intelligence quotient; n-number; RCT-randomized controlled

Applicability

ASD is characterized by significant heterogeneity within the population. There is substantial variation in both core and associated symptoms across and within children over time. Individual therapies are developed and tested to ameliorate specific symptoms or groups of symptoms, often in a fairly circumscribed subset of children. Ideally, research on therapies for ASD should target

specific children most likely to benefit from a particular focus; thus details on the population, intervention, comparator, outcomes, and setting (PICOS) for each intervention category are provided in Appendix G 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 interventions. In terms of followup for assessing durability of effects, most studies report on outcomes collected immediately post-treatment or within 3 months of treatment (roughly 75% of studies in the behavioral literature) although more studies than in our previous report attempt to assess impact over the course of much longer timespans. Additional research is needed on the degree to which changes observed during treatment translate to functional outcomes over time should treatment be discontinued. Importantly, ASD is often construed as a lifespan disorder and there has not yet been research assessing the long-term functional impact of treatment in childhood on lifespan development and functioning.

Studies of early intensive behavioral and developmental interventions were conducted primarily in preschool and young children (i.e., typically children initially ages 2–7) and as such questions remain about how these approaches apply to and benefit younger children diagnosed with or at-risk for ASD. 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). However, the availability and accessibility of the approaches studied are substantially limited in many community based settings. That is, the studies were often either conducted in highly controlled environments (e.g., university supported intervention trials) or the methodology was not well-described (i.e., non-manualized approaches). Thus, the generalizability of these methods to common practice should be assessed carefully. Even available manualized interventions require high degrees of specialization and training that will likely continue to make translation into common practice difficult.

Studies of parent training interventions and play-based interventions for preschool children, often emphasizing principles of ABA 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 offered manualized versions of training that can be adopted in other settings with appropriate training. Again the availability of providers capable of translating these programs may be limited in some community settings.

Most studies of social skills interventions targeted elementary school aged children (between 6 and 13 years old) with few studies targeting preschool age children, although such interventions may be important in this younger age group. Most also excluded children with IQ falling outside of the average range and certainly those below 70. 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 with gross average cognitive abilities and comorbid anxiety disorders. The effectiveness of both of these types of interventions in other groups of children with ASD is currently unknown.

Implications for Clinical and Policy Decisionmaking

This review may be useful to groups producing guidelines for practice, including professional organizations, state-level Medicaid medical directors, Federal entities and insurers. It provides an overview of available behavioral interventions and benefits observed to date that clinicians may find useful in making individual clinical recommendations to their patients and patient families. The larger body of literature of higher quality than in the previous review provides continued support for earlier conclusions that behavioral interventions can be beneficial for some children. Guidelines developed on the basis of the prior review warrant updating based on the level of new information and the degree to which strength of evidence shifted in the current review.

The evidence in favor of the efficacy of several types of behavioral interventions has increased, but there remains clinical uncertainty about how individual children will benefit from specific programs of intervention, which creates a challenge for implementation. Further, some interventions are limited in terms of the subset of the ASD population they are designed to treat (e.g., CBT and social skills interventions for older children with relatively intact cognitive abilities). In addition, pragmatic issues such as the availability of skilled providers and interventions themselves, resources to pay for interventions, as well as family considerations and preferences, may influence and guide treatment decisions.

Although there is increasing evidence that children with ASD who receive appropriate behavioral intervention can have substantial improvements in functioning, we have limited knowledge of the actual numbers of families able to access such services on a community level. Young children with ASD (below 36 months) are often eligible for services through Early Intervention (Part C) programs, with all states and eligible territories currently providing such programs. These systems presumably allow children to receive services based on risk prior to diagnosis as well as post-diagnosis, but services may range in intensity and focus. Children who are over age 3 often have access to additional services through their school district, but the nature of appropriate services provided within these systems varies. A majority of U.S. states (estimated at 34[182]) have enacted ASD insurance reform legislation that provides for specific access to evidence-based intervention services through private insurance. Again the availability and accessibility of resources for referral varies dramatically across communities

Limitations of the Review Process

We limited this update to comparative studies of behavioral interventions and included only those with at least 10 individuals. Thus, we did not include data from pre-post studies or those with a very small number of children. These would include single subject design studies that are helpful for understanding focused questions of short-term efficacy in individual children, and that may be useful for explicating mechanisms of action. These studies are less able to contribute to the body of evidence that we sought on population level and generalizable effects. Users of this review may want to take those studies into account as context when applying our findings. We limited our review to English language studies, not finding evidence that we were missing relevant research in other languages. We did not do a quantitative synthesis given the substantial heterogeneity of the literature base, but we recognize that this lack of synthesis may mitigate the ease with which the findings are applied. Therefore we have tried to provide substantial description that will help end users apply the findings.

Limitations of the Evidence Base

Despite improvements, the existing literature still has significant methodological concerns that in many ways continue to limit the strength of these conclusions.Evidence for the impact of intensive ABA based interventions on cognitive, language, adaptive skills, and ASD symptoms also highlights important limitations of current treatment modalities. First, even children who demonstrate clinically significant improvements in these areas often continue to display substantial impairment in these same and other areas. Second, not all children receiving intensive ABA-based intervention showed robust improvements in these domains. Thus, although this updated review makes it clearer that early intensive ABA-based intervention improves early impairment related to ASD, it is still challenging to describe the ultimate effect of these improvements in terms of long-term functional and adaptive outcomes on an individual level. Further, although children receiving early intensive developmental and behavioral intervention commonly display substantial improvements, the magnitude of these effects varies across studies and may indicate subgroups showing variable responses to particular interventions. Intervention response is likely moderated by both treatment and child factors. Despite multiple studies of early intensive treatments, intervention approaches still vary substantially, which makes it difficult to tease apart what these unique treatment and child factors may be. Further, researchers have not commonly utilized explicit methodologies or analyses to help elucidate moderation of treatment response across studies. As such, the current evidence is insufficient to adequately identify and target children most likely to benefit from specific interventions.

When examining treatment outcomes, many early intervention studies found that children in all groups improved on cognitive, adaptive, and autism symptom measures regardless of intervention type, although the degree of improvement was often greater in the treatment group. Results were often confounded by nonrandom assignment of participants, including assignment based on child characteristics (such as having the skills necessary to participate in intervention setting) or parental preference. The latter is especially problematic when outcomes are measured by parent report, given some evidence that parental stress influenced parent perceptions of child outcomes. Additionally, in most studies, both enrolled and control/waitlisted children were receiving concomitant interventions, the magnitude of which was inconsistently documented and controlled for in analyses.

A remaining significant challenge to interpreting the early intensive intervention literature relates to how interventions are described and implemented (see Appendix F for further characterization of the early intervention studies in this review). Although researchers are increasingly attempting to manualize approaches as well as operationalize and measure treatment fidelity, most of the body of literature categorized in this report as “early intensive behavioral and developmental intervention” remains an eclectic grouping. This category of intervention presently groups different treatment approaches (i.e., developmental, intensive behavioral, center based, and combinations), 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 many different outcome measurements over different periods of time (weeks to years). There are intrinsic challenges to manualizing intensive interventions to be delivered over the months and years for a very heterogeneous patient population. However, recent progress toward this end has shown that children will often respond differentially to early intensive approaches. Unfortunately, we do not yet understand how these specific intervention approaches differentially affect specific subgroups of children with ASD.

Few studies directly compared the effects of well-controlled treatment approaches, instead comparing interventions to non-specific "treatment as usual." Additionally, little data on the practical effectiveness or feasibility of these treatments beyond research studies exist, and questions remain about whether reported findings would generalize on a larger scale within communities. Furthermore, the studies conducted have used small samples, drastically different treatment approaches and duration, and different outcome measurements. Similarly, no studies in this category reported harms of intervention in terms of child, family, or system impact.

Although there was a fairly robust evidence base on CBT, the literature lacks head to head comparisons of treatment or controlled comparisons of combinations of treatments despite the fact that most children are undergoing multiple concurrent treatments. Although well designed, the sample sizes are quite modest. Additionally, the CBT approaches were modified for children with ASD and oftentimes manualized by the authors themselves, which highlights the need for replication by outside investigators. Lastly, the only study that did not show significant benefit in the CBT intervention group compared with it to an active treatment control as opposed to a waitlist or treatment as usual control.[161] This suggests that more studies including active control groups are needed to examine if CBT reduces anxiety more than other treatment modalities.

Research Gaps and Needs

Several behavioral treatment approaches report positive outcomes in children with ASD, increasingly using rigorous designs. Despite this recent and improved rigor, treatments remain understudied. In addition, very few studies have attempted to systematically replicate findings of previous work.

Given the heterogeneity of the expression of ASD within and across children, a critical area for further research is understanding which children are likely to benefit from particular interventions. To date, studies have failed adequately to characterize interventions or children receiving intervention such that we can better understand which children are most likely to experience positive outcomes and why. Further, our understanding of early indicators of treatment response is extremely limited, such that evidence-based changes in treatment planning based on an observed response or lack thereof are not possible. This is important to parents, providers, and families as they often want to know not only when a treatment is working, but when limited benefit of treatments may suggest pursuing other treatment options.

Again the accumulated evidence base suggests that while children receiving early intensive intervention will demonstrate substantial gains in several areas of functioning (e.g., cognitive ability, language, adaptive, ASD symptoms) on a group level, not all children receiving early intensive intervention will demonstrate robust gains. Currently, the evidence suggests some children will show dramatic improvement, others will display robust improvement in some areas with continued areas of vulnerability in others, and other children will show more moderated response to treatment overall. It is also unclear how similar groups of children will perform at differing levels of intensity of interventions or different treatment approaches and methods. Child characteristics like baseline cognitive, language, adaptive skill, and ASD symptoms may correlate with treatment outcome; however, such correlational data provides limited information in making predictions of what treatments will work best for individual children. Further, intensive, comprehensive intervention strategies are by their very nature often multi-component. Data on whether specific functional components of the interventions drive effectiveness are currently unavailable. Finally, the intervention research often fails to describe whether treatment effect is modified by family, culture, available resources, and stress. Early intensive behavioral

and developmental approaches therefore warrant further research to understand individual response and benefit in the short and long-term across heterogeneous populations.

A primary methodological concern relates to outcome measurement. Intervention research in the field of ASD has often relied on various and differing ways of marking change, which has limited our ability to understand change within and across individual studies.[183] The manner in which outcomes are operationalized in many studies is often problematic as well. Quite often outcome is operationalized and studied in terms of change on standardized measures of ability referencing normative populations (i.e., IQ measurement, adaptive behavior scores), which may not necessarily be an appropriate or adequate method for measuring or predicting early treatment response, changes in quality of life, or long-term functional outcomes. Such measurement, while providing data that can be compared to that in typically developing populations, may unfortunately miss important information about changes that are relevant within the ASD population . More simply, it is unclear that measures of cognitive ability, language, and ASD diagnostic symptoms are actually ideal or adequately sensitive methods for measuring frequency, intensity, and impairment in children with ASD. Research on appropriate methods to capture meaningful change will be critical to advance our understanding of behavioral interventions.

In some aspects of the literature treatments with some replicated studies have emerged. Specifically both social skills interventions and cognitive behavioral interventions for anxiety have demonstrated short-term benefit for some children with ASD. However, this literature focuses almost entirely on older children with ASD and intact cognitive skills. Understanding the impact or lack thereof of such interventions for others with ASD is important. Further, this work has often relied on parent or teacher reports of functioning to gauge change. Such reporting may be useful as a preliminary index or potentially as a component of a broader measurement strategy attempting to index change, but reliance these ratings provides only an intermediate and often biased assessment of change, with potentially very limited value to understanding how interventions translate in to meaningful long-term functional outcomes.

Because the treatment process for ASD is typically intensive and often requires highly specific and well-trained individuals to deliver to fidelity, questions of feasibility and accessibility are pertinent but largely understudied. Explicit evaluation of treatments of highest impact in community settings as well as studies explicitly evaluating settings and providers would benefit our ability to understand impact and implementation.

Finally, this literature lacks comparisons of interventions and combinations of interventions (e.g., medical interventions, with behavioral interventions, with educational interventions, with allied health interventions), despite the fact that most children are undergoing multiple concurrent treatments.

Conclusions

Since our previous review in 2011, we have seen a significant increase in the quality of studies investigating behavioral interventions. Of the 45 comparative studies of behavioral interventions (29 RCTs) in the 2011 review, we considered only two as good quality. Among the new studies of behavioral interventions described in this current review, 16 studies are good quality, and 37 of the 51 included studies are RCTs.

These improvements allow us to make some stronger conclusions about certain elements of the behavioral intervention literature. Considerable and consistent evidence suggests that early behavioral and developmental intervention based on the principles of ABA delivered in intensive ($\geq$15 hours per week) and comprehensive (i.e., addressing numerous areas of functioning) form

significantly affects the development of children with ASD. The current review includes RCTs of the UCLA/Lovaas focused approach, a developmentally focused ESDM approach, a school delivered training (LEAP), as well as prospective comparisons of eclectic variants of ABA approaches. Across approaches, children receiving early intensive behavioral and developmental interventions demonstrate improvements in cognitive, language, adaptive, and ASD impairments compared with children receiving low-intensity interventions and eclectic non-ABA based intervention approaches.

Since our previous review, there have also been substantially more studies of well-controlled low intensity interventions including parent training aimed at social communication skills. This growing evidence base suggests that such interventions may have positive results in very young children's social communication and language use. However, although parent training programs certainly modified parenting behaviors during interactions, data are more limited about their ability to improve broad developmental skills (such as cognition, adaptive behavior, and ASD symptom severity) beyond short-term language gains for some children.

A growing number of studies of improved quality have demonstrated benefit of social skills interventions on at least one outcome measure, but a lack of consistency in the interventions studied and outcome measures utilized makes it difficult to understand the consistency or precision of impact across intervention modes. Further, social skills interventions have also been limited to a restricted range of children to date.

A growing evidence base suggests that children receiving targeted play-based interventions (e.g., joint attention, imitation, play-based interventions) demonstrate improvements in early social communication skills. Children receiving targeted joint attention packages in combination with other interventions show substantial improvements in joint attention and language skills over time. Young children in play-based interventions may display short-term improvements in early play, imitation, joint attention, and interaction skills. However, there is not substantial evidence that these short-term improvements are linked to broader indices of change over time.

CBT for associated conditions such as anxiety has the largest number of high quality studies in the current review. A strong evidence base suggests that school-aged children with average to above average intelligence and comorbid anxiety symptoms receiving manualized CBT therapy show substantial improvements in anxiety compared with wait-list controls. Importantly, CBT therapy is often targeted, delimited, and has numerous manualized approaches available for study. Further, CBT intervention for anxiety has been studied within a restricted population to date (e.g., average to above average cognitive skills with comorbid anxiety).

In sum, a growing evidence base suggests that behavioral interventions are associated with positive outcomes for children with ASD. Despite improvements in the quality of the included literature, a need remains for studies of interventions across settings and continued improvements in methodologic rigor. Substantial scientific advances are needed to move toward an enhanced understanding of which interventions are most effective for specific children with ASD.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington DC: American Psychiatric Association, 2013.
2. Manning-Courtney P, Murray D, Currans K, et al. Autism spectrum disorders. Curr Probl Pediatr Adolesc Health Care 2013 Jan;43(1):2-11. PMID: 23332397.
3. Ozonoff S, Goodlin-Jones BL, Solomon M. Evidence-based assessment of autism spectrum disorders in children and adolescents. J Clin Child Adolesc Psychol 2005 Sep;34(3):523-40. PMID: 16083393.
4. Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. Pediatrics 2009 May;123(5):1383-91. PMID: 19403506.
5. Myers SM, Johnson CP. Management of children with autism spectrum disorders. Pediatrics 2007 Nov;120(5):1162-82. PMID: 17967921.
6. Myers SM. The status of pharmacotherapy for autism spectrum disorders. Expert Opin Pharmacother 2007 Aug;8(11):1579-603. PMID: 17685878.
7. Autism, Developmental Disabilities Monitoring Network Surveillance Year Principal I, Centers for Disease C, et al. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ 2012 Mar 30;61(3):1-19. PMID: 22456193.
8. Fecteau S, Mottron L, Berthiaume C, et al. Developmental changes of autistic symptoms. Autism 2003 Sep;7(3):255-68. PMID: 14516059.
9. Shattuck PT, Seltzer MM, Greenberg JS, et al. Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. J Autism Dev Disord 2007 Oct;37(9):1735-47. PMID: 17146700.
10. McGovern CW, Sigman M. Continuity and change from early childhood to adolescence in autism. J Child Psychol Psychiatry 2005 Apr;46(4):401-8. PMID: 15819649.
11. Seltzer MM, Shattuck P, Abbeduto L, et al. Trajectory of development in adolescents and adults with autism. Ment Retard Dev Disabil Res Rev 2004;10(4):234-47. PMID: 15666341.
12. Ballaban-Gil K, Rapin I, Tuchman R, et al. Longitudinal examination of the behavioral, language, and social changes in a population of adolescents and young adults with autistic disorder. Pediatr Neurol 1996 Oct;15(3):217-23. PMID: 8916159.
13. Billstedt E, Gillberg C, Gillberg C. Autism after Adolescence: Population-Based 13- to 22-Year Follow-Up Study of 120 Individuals with Autism Diagnosed in Childhood. Journal of Autism and Developmental Disorders 2005 Jun;35(3):351-60. PMID: EJ735642.
14. Eaves LC, Ho HH. Young Adult Outcome of Autism Spectrum Disorders. Journal of Autism and Developmental Disorders 2008 Apr;38(4):739-47. PMID: EJ788752.
15. Howlin P, Goode S, Hutton J, et al. Adult outcome for children with autism. J Child Psychol Psychiatry 2004 Feb;45(2):212-29. PMID: 14982237.
16. Taylor JL, Seltzer MM. Employment and post-secondary educational activities for young adults with autism spectrum disorders during the transition to adulthood. J Autism Dev Disord 2011 May;41(5):566-74. PMID: 20640591.
17. Ganz ML. The lifetime distribution of the incremental societal costs of autism. Arch Pediatr Adolesc Med 2007 Apr;161(4):343-9. PMID: 17404130.
18. Folstein SE, Rosen-Sheidley B. Genetics of autism: complex aetiology for a heterogeneous disorder. Nat Rev Genet 2001 Dec;2(12):943-55. PMID: 11733747.

19. Bailey A, Le Couteur A, Gottesman I, et al. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 1995 Jan;25(1):63-77. PMID: 7792363.
20. Marshall CR, Scherer SW. Detection and characterization of copy number variation in autism spectrum disorder. Methods Mol Biol 2012;838:115-35. PMID: 22228009.
21. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci 2011 Sep;15(9):409-16. PMID: 21855394.
22. Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011 Nov;68(11):1095-102. PMID: 21727249.
23. Bristol MM, Cohen DJ, Costello EJ, et al. State of the science in autism: report to the National Institutes Health. J Autism Dev Disord 1996 Apr;26(2):121-54. PMID: 8744475.
24. Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 2012 May;129(5):e1121-8. PMID: 22492772.
25. Dodds L, Fell DB, Shea S, et al. The role of prenatal, obstetric and neonatal factors in the development of autism. J Autism Dev Disord 2011 Jul;41(7):891-902. PMID: 20922473.
26. Sandin S, Hultman CM, Kolevzon A, et al. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2012 May;51(5):477-86 e1. PMID: 22525954.
27. Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. Autism Res 2010 Feb;3(1):30-9. PMID: 20143326.
28. Bhandari A, Sandlow JI, Brannigan RE. Risks to offspring associated with advanced paternal age. J Androl 2011 Mar-Apr;32(2):121-2. PMID: 20467047.
29. Cheslack-Postava K, Liu K, Bearman PS. Closely spaced pregnancies are associated with increased odds of autism in California sibling births. Pediatrics 2011 Feb;127(2):246-53. PMID: 21220394.
30. Gunnes N, Suren P, Bresnahan M, et al. Interpregnancy interval and risk of autistic disorder. Epidemiology 2013 Nov;24(6):906-12. PMID: 24045716.
31. Shelton JF, Hertz-Picciotto I, Pessah IN. Tipping the balance of autism risk: potential mechanisms linking pesticides and autism. Environ Health Perspect 2012 Jul;120(7):944-51. PMID: 22534084.
32. Schultz ST. Does thimerosal or other mercury exposure increase the risk for autism? A review of current literature. Acta Neurobiol Exp (Wars) 2010;70(2):187-95. PMID: 20628442.
33. Ozonoff S, Young GS, Carter A, et al. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. Pediatrics 2011 Sep;128(3):e488-95. PMID: 21844053.
34. Gronborg TK, Schendel DE, Parner ET. Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study. JAMA Pediatr 2013 Oct;167(10):947-53. PMID: 23959427.
35. Seida JK, Ospina MB, Karkhaneh M, et al. Systematic reviews of psychosocial interventions for autism: an umbrella review. Dev Med Child Neurol 2009 Feb;51(2):95-104. PMID: 19191842.
36. Ospina MB, Krebs Seida J, Clark B, et al. Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. PLoS One 2008;3(11):e3755. PMID: 19015734.
37. Parr J. Autism. Clin Evid (Online) 2008;2008PMID: 19450315.

38. National Autism Center. National Standards Report. Randolph, MA; National Autism Center, 2009. Available at: http://www.nationalautismcenter.org/pdf/NAC%20Standards%20Report.pdf
39. Warren Z, Veenstra-VanderWeele J, Stone W, Bruzek JL, Nahmias AS, Foss-Feig JH, Jerome RN, Krishnaswami S, Sathe NA, Glasser AM, Surawicz T, McPheeters ML. Therapies for Children With Autism Spectrum Disorders. Comparative Effectiveness Review No. 26. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 11-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.
40. Committee on Educational Interventions for Children with Autism. Educating Children with Autism Washington DC: Press; 2001.
41. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. J Consult Clin Psychol 1987 Feb;55(1):3-9. PMID: 3571656.
42. Bryson SE, Rogers SJ, Fombonne E. Autism spectrum disorders: early detection, intervention, education, and psychopharmacological management. Can J Psychiatry 2003 Sep;48(8):506-16. PMID: 14574826.
43. Rogers SJ, Vismara LA. Evidence-Based Comprehensive Treatments for Early Autism. Journal of Clinical Child and Adolescent Psychology 2008 Jan;37(1):8-38. PMID: EJ791173.
44. Reichow B, Wolery M. Comprehensive Synthesis of Early Intensive Behavioral Interventions for Young Children with Autism Based on the UCLA Young Autism Project Model. Journal of Autism and Developmental Disorders 2009 Jan;39(1):23-41. PMID: EJ822609.
45. Reichow B, Barton EE, Boyd BA, et al. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev 2012;10:CD009260. PMID: 23076956.
46. Warren Z, McPheeters ML, Sathe N, et al. A systematic review of early intensive intervention for autism spectrum disorders. Pediatrics 2011 May;127(5):e1303-11. PMID: 21464190.
47. Spreckley M, Boyd R. Efficacy of Applied Behavioral Intervention in Preschool Children with Autism for Improving Cognitive, Language, and Adaptive Behavior: A Systematic Review and Meta-analysis. J Pediatr 2008 Oct 22PMID: 18950798.
48. McConachie H, Diggle T. Parent implemented early intervention for young children with autism spectrum disorder: a systematic review. J Eval Clin Pract 2007 Feb;13(1):120-9. PMID: 17286734.
49. Eldevik S, Hastings RP, Hughes JC, et al. Meta-analysis of Early Intensive Behavioral Intervention for children with autism. J Clin Child Adolesc Psychol 2009 May;38(3):439-50. PMID: 19437303.
50. Howlin P, Magiati I, Charman T. Systematic Review of Early Intensive Behavioral Interventions for Children with Autism. American Journal on Intellectual and Developmental Disabilities 2009 Jan;114(1):23-41. PMID: EJ824908.
51. Makrygianni MK, Reed P. A Meta-Analytic Review of the Effectiveness of Behavioural Early Intervention Programs for Children with Autistic Spectrum Disorders. 2010;4:577-93. PMID: 742844642; EJ886516.
52. Virues-Ortega J. Applied behavior analytic intervention for autism in early childhood: meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. Clin Psychol Rev 2010 Jun;30(4):387-99. PMID: 20223569.

53. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol 2010 May;63(5):502-12. PMID: 18823754.
54. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Public ation No. 10(13)-EHC063-EF. Rockville, MD: Agency for Healthcare Researchand Quality. September 2013. Chapters available at: www.effectivehealthcare.ahrq.gov
55. Berkman ND, Lohr KN, Ansari M, McDonagh M, Balk E, Whitlock E, Reston J, Bass E, Butler M, Gartlehner G, Hartling L, Kane R, McPheeters M, Morgan L, Morton SC, Sista P, Viswanathan M, Chang S. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update RTI-UNC Evidence-based Practice Center, Contract No. HHSA-290-2007-10056-I-EPC3, Task Order #5.
56. Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. Am J Ment Retard 2000 Jul;105(4):269-85. PMID: 10934569.
57. Eldevik S, Eikeseth S, Jahr E, et al. Effects of low-intensity behavioral treatment for children with autism and mental retardation. J Autism Dev Disord 2006 Feb;36(2):211-24. PMID: 16477514.
58. Farrell P, Trigonaki N, Webster D. An exploratory evaluation of two early intervention programmes for young children with autism. Educational and Child Psychology 2005;22(4):29-40. PMID: 2006-03789-003.
59. Cohen H, Amerine-Dickens M, Smith T. Early intensive behavioral treatment: replication of the UCLA model in a community setting. J Dev Behav Pediatr 2006 Apr;27(2 Suppl):S145-55. PMID: 16685181.
60. Howard JS, Sparkman CR, Cohen HG, et al. A comparison of intensive behavior analytic and eclectic treatments for young children with autism. Res Dev Disabil 2005 Jul-Aug;26(4):359-83. PMID: 15766629.
61. Zachor DA, Ben-Itzchak E, Rabinovich A-L, et al. Change in Autism Core Symptoms with Early Intervention: predictors and outcomes. Research in Autism Spectrum Disorders 2009;3:967-76. PMID: EJ796901.
62. Zachor DA, Ben-Itzchak E, Rabinovich A-L, et al. Change in autism core symptoms with intervention. Research in Autism Spectrum Disorders 2007;1(4):304-17.
63. Reed P, Osborne LA, Corness M. Brief report: relative effectiveness of different home-based behavioral approaches to early teaching intervention. J Autism Dev Disord 2007 Oct;37(9):1815-21. PMID: 17180714.
64. Eikeseth S, Smith T, Jahr E, et al. Intensive behavioral treatment at school for 4- to 7-year-old children with autism. A 1-year comparison controlled study. Behav Modif 2002 Jan;26(1):49-68. PMID: 11799654.
65. Eikeseth S, Smith T, Jahr E, et al. Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7: a comparison controlled study. Behav Modif 2007 May;31(3):264-78. PMID: 17438342.
66. Hayward D, Eikeseth S, Gale C, et al. Assessing progress during treatment for young children with autism receiving intensive behavioural interventions. Autism 2009 Nov;13(6):613-33. PMID: 19933766.

67. Eikeseth S, Hayward D, Gale C, et al. Intensity of Supervision and Outcome for Preschool Aged Children Receiving Early and Intensive Behavioral Interventions: A Preliminary Study. Research in Autism Spectrum Disorders 2009 Jan;3(1):67-73. PMID: EJ820616.
68. Drew A, Baird G, Baron-Cohen S, et al. A pilot randomised control trial of a parent training intervention for pre-school children with autism. Preliminary findings and methodological challenges. Eur Child Adolesc Psychiatry 2002 Dec;11(6):266-72. PMID: 12541005.
69. Stahmer AC, Gist K. The effects of an accelerated parent education program on technique mastery and child outcome. Journal of Positive Behavior Interventions 2001 Spr;3(2):75-82. PMID: 2001-17079-002.
70. Green J, Charman T, McConachie H, et al. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. Lancet 2010 May 20PMID: 20494434.
71. Aldred C, Green J, Adams C. A new social communication intervention for children with autism: pilot randomised controlled treatment study suggesting effectiveness. J Child Psychol Psychiatry 2004 Nov;45(8):1420-30. PMID: 15482502.
72. Dawson G, Rogers S, Munson J, et al. Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model. Pediatrics 2010 January 2010.
73. McConachie H, Randle V, Hammal D, et al. A controlled trial of a training course for parents of children with suspected autism spectrum disorder. J Pediatr 2005 Sep;147(3):335-40. PMID: 16182672.
74. Sallows GO, Graupner TD. Intensive behavioral treatment for children with autism: four-year outcome and predictors. Am J Ment Retard 2005 Nov;110(6):417-38. PMID: 16212446.
75. Peters-Scheffer N, Didden R, Mulders M, et al. Low intensity behavioral treatment supplementing preschool services for young children with autism spectrum disorders and severe to mild intellectual disability. Res Dev Disabil 2010 Nov-Dec;31(6):1678-84. PMID: 20627451.
76. Eldevik S, Hastings RP, Jahr E, et al. Outcomes of behavioral intervention for children with autism in mainstream pre-school settings. J Autism Dev Disord 2012 Feb;42(2):210-20. PMID: 21472360.
77. Eikeseth S, Klintwall L, Jahr E, et al. Outcome for Children with Autism Receiving Early and Intensive Behavioral Intervention in Mainstream Preschool and Kindergarten Settings. Research in Autism Spectrum Disorders 2012;6(2):829-35. PMID: 1023529557; EJ966831.
78. Kovshoff H, Hastings RP, Remington B. Two-year outcomes for children with autism after the cessation of early intensive behavioral intervention. Behav Modif 2011 Sep;35(5):427-50. PMID: 21586502.
79. Remington B, Hastings RP, Kovshoff H, et al. Early intensive behavioral intervention: outcomes for children with autism and their parents after two years. Am J Ment Retard 2007 Nov;112(6):418-38. PMID: 17963434.
80. Itzchak EB, Zachor DA. Who Benefits from Early Intervention in Autism Spectrum Disorders? Research in Autism Spectrum Disorders 2011;5(1):345-50. PMID: 762466666; EJ900428.
81. Zachor DA, Itzchak EB. Treatment Approach, Autism Severity and Intervention Outcomes in Young Children. Research in Autism Spectrum Disorders 2010;4(3):425-32. PMID: 742864417; EJ878590.
82. Boyd BA, Hume K, McBee MT, et al. Comparative Efficacy of LEAP, TEACCH and Non-Model-Specific Special Education Programs for Preschoolers with Autism Spectrum Disorders. J Autism Dev Disord 2013 Jun 28PMID: 23812661.

83. Strain PS, Bovey EH. Randomized, Controlled Trial of the Leap Model of Early Intervention for Young Children with Autism Spectrum Disorders. Topics in Early Childhood Special Education 2011;31(3):133-54. PMID: 964193023; EJ942105.
84. Dawson G, Jones EJ, Merkle K, et al. Early behavioral intervention is associated with normalized brain activity in young children with autism. J Am Acad Child Adolesc Psychiatry 2012 Nov;51(11):1150-9. PMID: 23101741.
85. Flanagan HE, Perry A, Freeman NL. Effectiveness of large-scale community-based intensive Behavioral Intervention: A waitlist comparison study exploring outcomes and predictors. Research in Autism Spectrum Disorders 2012;6(2):673-82. PMID: 928983882; 2012-03990-011.
86. Shine R, Perry A. The relationship between parental stress and intervention outcome of children with autism. Journal on Developmental Disabilities 2010;16(2):64-6. PMID: 888748756; 2011-15965-007.
87. Freeman N, Perry A. Outcomes of intensive behavioural intervention in the Toronto Preschool Autism Service. Journal on Developmental Disabilities 2010;16(2):17-32. PMID: 888750958; 2011-15965-003.
88. Perry A, Cummings A, Geier JD, et al. Effectiveness of Intensive Behavioral Intervention in a Large, Community-Based Program. Research in Autism Spectrum Disorders 2008 Oct;2(4):621-42. PMID: EJ810176.
89. Perry A, Cummings A, Geier JD, et al. Predictors of Outcome for Children Receiving Intensive Behavioral Intervention in a Large, Community-Based Program. Research in Autism Spectrum Disorders 2011;5(1):592-603. PMID: 815956916; EJ900402.
90. Pajareya K, Nopmaneejumruslers K. A pilot randomized controlled trial of DIR/Floortime parent training intervention for pre-school children with autistic spectrum disorders. Autism 2011 Sep;15(5):563-77. PMID: 21690083.
91. Carter AS, Messinger DS, Stone WL, et al. A randomized controlled trial of Hanen's 'More Than Words' in toddlers with early autism symptoms. J Child Psychol Psychiatry 2011 Jul;52(7):741-52. PMID: 21418212.
92. Oosterling I, Visser J, Swinkels S, et al. Randomized controlled trial of the focus parent training for toddlers with autism: 1-year outcome. J Autism Dev Disord 2010 Dec;40(12):1447-58. PMID: 20440639.
93. Reed P, Osborne L. Impact of Severity of Autism and Intervention Time-Input on Child Outcomes: Comparison across Several Early Interventions. British Journal of Special Education 2012;39(3):130-6. PMID: 1140138033; EJ979673.
94. Roberts J, Williams K, Carter M, et al. A Randomised Controlled Trial of Two Early Intervention Programs for Young Children with Autism: Centre-Based with Parent Program and Home-Based. Research in Autism Spectrum Disorders 2011;5(4):1553-66. PMID: 881469872; EJ927523.
95. McConkey R, Truesdale-Kennedy M, Crawford H, et al. Preschoolers with Autism Spectrum Disorders: Evaluating the Impact of a Home-Based Intervention to Promote Their Communication. Early Child Development and Care 2010;180(3):299-315. PMID: 742873127; EJ882838.
96. Rogers SJ, Estes A, Lord C, et al. Effects of a brief Early Start Denver Model (ESDM)–based parent intervention on toddlers at risk for autism spectrum disorders: A randomized controlled trial. Journal of the American Academy of Child & Adolescent Psychiatry 2012;51(10):1052-65. PMID: 1136157899; 2012-26793-013.

97. Wong VCN, Kwan QK. Randomized controlled trial for early intervention for autism: A pilot study of the Autism 1-2-3 project. Journal of Autism and Developmental Disorders 2010;40(6):677-88. PMID: 622202972; 2010-09318-003.
98. Keen D, Couzens D, Muspratt S, et al. The effects of a parent-focused intervention for children with a recent diagnosis of autism spectrum disorder on parenting stress and competence. Research in Autism Spectrum Disorders 2010;4(2):229-41. PMID: 856409394; 2011-03277-009.
99. Strauss K, Vicari S, Valeri G, et al. Parent inclusion in Early Intensive Behavioral Intervention: the influence of parental stress, parent treatment fidelity and parent-mediated generalization of behavior targets on child outcomes. Res Dev Disabil 2012 Mar-Apr;33(2):688-703. PMID: 22188793.
100. Fava L, Strauss K, Valeri G, et al. The Effectiveness of a Cross-Setting Complementary Staff- and Parent-Mediated Early Intensive Behavioral Intervention for Young Children with ASD. Research in Autism Spectrum Disorders 2011;5(4):1479-92. PMID: 881460693; EJ927555.
101. Landa RJ, Holman KC, O'Neill AH, et al. Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: a randomized controlled trial. J Child Psychol Psychiatry 2011 Jan;52(1):13-21. PMID: 21126245.
102. Landa RJ, Kalb LG. Long-term outcomes of toddlers with autism spectrum disorders exposed to short-term intervention. Pediatrics 2012 Nov;130 Suppl 2:S186-90. PMID: 23118250.
103. Aldred C, Green J, Emsley R, et al. Mediation of treatment effect in a communication intervention for pre-school children with autism. Journal of Autism and Developmental Disorders 2012;42(3):447-54. PMID: 928983846; 2012-04398-013.
104. Reed P, Osborne LA, Corness M. The Real-World Effectiveness of Early Teaching Interventions for Children with Autism Spectrum Disorder. Exceptional Children 2007 Sum;73(4):417-33. PMID: EJ817513.
105. Reed P, Osborne LA, Corness M. Effectiveness of Special Nursery Provision for Children with Autism Spectrum Disorders. Autism: The International Journal of Research and Practice 2010;14(1):67-82. PMID: EJ872182.
106. Banda DR, Grimmett E. Enhancing Social and Transition Behaviors of Persons with Autism through Activity Schedules: A Review. Education and Training in Developmental Disabilities 2008 Sep;43(3):324-33. PMID: EJ804646.
107. Quirmbach LM, Lincoln AJ, Feinberg-Gizzo MJ, et al. Social stories: mechanisms of effectiveness in increasing game play skills in children diagnosed with autism spectrum disorder using a pretest posttest repeated measures randomized control group design. J Autism Dev Disord 2009 Feb;39(2):299-321. PMID: 18704672.
108. Lopata C, Thomeer ML, Volker MA, et al. Effectiveness of a manualized summer social treatment program for high-functioning children with autism spectrum disorders. J Autism Dev Disord 2008 May;38(5):890-904. PMID: 18058012.
109. Solomon M, Goodlin-Jones BL, Anders TF. A social adjustment enhancement intervention for high functioning autism, Asperger's syndrome, and pervasive developmental disorder NOS. J Autism Dev Disord 2004 Dec;34(6):649-68. PMID: 15679185.
110. Frankel F, Myatt R, Sugar C, et al. A Randomized Controlled Study of Parent-assisted Children's Friendship Training with Children having Autism Spectrum Disorders. J Autism Dev Disord 2010 Jan 8PMID: 20058059.

111. Beaumont R, Sofronoff K. A multi-component social skills intervention for children with Asperger syndrome: the Junior Detective Training Program. J Child Psychol Psychiatry 2008 Jul;49(7):743-53. PMID: 18503531.
112. Kroeger KA, Schultz JR, Newsom C. A Comparison of Two Group-Delivered Social Skills Programs for Young Children with Autism. Journal of Autism and Developmental Disorders 2007 May;37(5):808-17. PMID: EJ763373.
113. Owens G, Granader Y, Humphrey A, et al. LEGO therapy and the social use of language programme: an evaluation of two social skills interventions for children with high functioning autism and Asperger Syndrome. J Autism Dev Disord 2008 Nov;38(10):1944-57. PMID: 18566882.
114. Golan O, Ashwin E, Granader Y, et al. Enhancing Emotion Recognition in Children with Autism Spectrum Conditions: An Intervention Using Animated Vehicles with Real Emotional Faces. Journal of Autism and Developmental Disorders 2010 Mar;40(3):269-79. PMID: EJ873008.
115. Legoff DB, Sherman M. Long-Term Outcome of Social Skills Intervention Based on Interactive LEGO[C] Play. Autism: The International Journal of Research & Practice 2006;10(4):317-29. PMID: EJ741609.
116. Williams BT, Gray KM, Tonge BJ. Teaching Emotion Recognition Skills to Young Children with Autism: A Randomised Controlled Trial of an Emotion Training Programme. Journal of Child Psychology and Psychiatry 2012;53(12):1268-76. PMID: 1312422882; EJ988275.
117. Koenig K, White SW, Pachler M, et al. Promoting social skill development in children with pervasive developmental disorders: a feasibility and efficacy study. J Autism Dev Disord 2010 Oct;40(10):1209-18. PMID: 20204689.
118. Kasari C, Rotheram-Fuller E, Locke J, et al. Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. J Child Psychol Psychiatry 2012 Apr;53(4):431-9. PMID: 22118062.
119. DeRosier ME, Swick DC, Davis NO, et al. The efficacy of a Social Skills Group Intervention for improving social behaviors in children with High Functioning Autism Spectrum disorders. J Autism Dev Disord 2011 Aug;41(8):1033-43. PMID: 21042870.
120. Lopata C, Thomeer ML, Volker MA, et al. RCT of a manualized social treatment for high-functioning autism spectrum disorders. J Autism Dev Disord 2010 Nov;40(11):1297-310. PMID: 20232240.
121. Begeer S, Gevers C, Clifford P, et al. Theory of mind training in children with autism: A randomized controlled trial. Journal of Autism and Developmental Disorders 2011;41(8):997-1006. PMID: 883434155; 2011-14964-002.
122. Lerner MD, Mikami AY. A preliminary randomized controlled trial of two social skills interventions for youth with high-functioning autism spectrum disorders. Focus on Autism and Other Developmental Disabilities 2012;27(3):147-57. PMID: 1284065811; 2012-22099-002.
123. Sutton SK, Burnette CP, Mundy PC, et al. Resting cortical brain activity and social behavior in higher functioning children with autism. J Child Psychol Psychiatry 2005 Feb;46(2):211-22. PMID: 15679529.
124. Castorina LL, Negri LM. The inclusion of siblings in social skills training groups for boys with Asperger syndrome. J Autism Dev Disord 2011 Jan;41(1):73-81. PMID: 20461452.
125. Young RL, Posselt M. Using the transporters DVD as a learning tool for children with Autism Spectrum Disorders (ASD). J Autism Dev Disord 2012 Jun;42(6):984-91. PMID: 21822764.

126. Thomeer ML, Lopata C, Volker MA, et al. Randomized clinical trial replication of a psychosocial treatment for children with high-functioning autism spectrum disorders. Psychology in the Schools 2012;49(10):942-54. PMID: 1267035401; 2012-30641-004.
127. Cihak DF, Smith CC, Cornett A, et al. The Use of Video Modeling with the Picture Exchange Communication System to Increase Independent Communicative Initiations in Preschoolers with Autism and Developmental Delays. Focus on Autism and Other Developmental Disabilities 2012;27(1):3-11. PMID: 968109134; EJ956535.
128. White SW, Koenig K, Scahill L. Group Social Skills Instruction for Adolescents with High-Functioning Autism Spectrum Disorders. Focus on Autism and Other Developmental Disabilities 2010;25(4):209-19. PMID: 851229043; EJ910635.
129. Solomon M, Ono M, Timmer S, et al. The effectiveness of parent-child interaction therapy for families of children on the autism spectrum. J Autism Dev Disord 2008 Oct;38(9):1767-76. PMID: 18401693.
130. Kasari C, Paparella T, Freeman S, et al. Language outcome in autism: randomized comparison of joint attention and play interventions. J Consult Clin Psychol 2008 Feb;76(1):125-37. PMID: 18229990.
131. Kasari C, Freeman S, Paparella T. Joint attention and symbolic play in young children with autism: a randomized controlled intervention study. J Child Psychol Psychiatry 2006 Jun;47(6):611-20. PMID: 16712638.
132. Field T, Sanders C, Nadel J. Children with autism display more social behaviors after repeated imitation sessions. Autism 2001 Sep;5(3):317-23. PMID: 11708590.
133. Heimann M, Laberg KE, Nordoen B. Imitative Interaction Increases Social Interest and Elicited Imitation in Non-verbal Children with Autism. Infant and Child Development. Special Issue: Imitation and Socio-Emotional Processes: Implications for Communicative Development and Interventions 2006 May-Jun;15(3):297-309. PMID: 2006-08875-008.
134. Escalona A, Field T, Nadel J, et al. Brief report: Imitation effects on children with autism. Journal of Autism and Developmental Disorders 2002 Apr;32(2):141-4. PMID: 2002-13970-009.
135. Gulsrud AC, Kasari C, Freeman S, et al. Children with autism's response to novel stimuli while participating in interventions targeting joint attention or symbolic play skills. Autism 2007 Nov;11(6):535-46. PMID: 2007-17145-006.
136. Whittingham K, Sofronoff K, Sheffield J, et al. Stepping Stones Triple P: An RCT of a Parenting Program with Parents of a Child Diagnosed with an Autism Spectrum Disorder. Journal of Abnormal Child Psychology 2009 May;37(4):469-80. PMID: EJ834945.
137. Whittingham K, Sofronoff K, Sheffield J, et al. Do Parental Attributions Affect Treatment Outcome in a Parenting Program? An Exploration of the Effects of Parental Attributions in an RCT of Stepping Stones Triple P for the ASD Population. Research in Autism Spectrum Disorders 2009 Jan;3(1):129-44. PMID: EJ820612.
138. Kasari C, Gulsrud A, Freeman S, et al. Longitudinal follow-up of children with autism receiving targeted interventions on joint attention and play. J Am Acad Child Adolesc Psychiatry 2012 May;51(5):487-95. PMID: 22525955.
139. Lawton K, Kasari C. Brief Report: Longitudinal Improvements in the Quality of Joint Attention in Preschool Children with Autism. Journal of Autism and Developmental Disorders 2012;42(2):307-12. PMID: 964190966; EJ954567.
140. Kasari C, Gulsrud AC, Wong C, et al. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. Journal of Autism and Developmental Disorders 2010;40(9):1045-56. PMID: 754055821; 2010-17107-001.

141. Goods KS, Ishijima E, Chang Y-C, et al. Preschool Based JASPER Intervention in Minimally Verbal Children with Autism: Pilot RCT. Journal of Autism and Developmental Disorders 2013 May 2013;43(5):1050-6. PMID: 1361838997; EJ1000575.
142. Ingersoll B. Brief report: effect of a focused imitation intervention on social functioning in children with autism. J Autism Dev Disord 2012 Aug;42(8):1768-73. PMID: 22146934.
143. Ingersoll B. Brief report: Pilot randomized controlled trial of reciprocal imitation training for teaching elicited and spontaneous imitation to children with autism. Journal of Autism and Developmental Disorders 2010;40(9):1154-60. PMID: 754055593; 2010-17107-012.
144. Venker CE, McDuffie A, Weismer SE, et al. Increasing Verbal Responsiveness in Parents of Children with Autism: A Pilot Study. Autism: The International Journal of Research and Practice 2012;16(6):568-85. PMID: 1238188272; EJ984594.
145. Kaale A, Smith L, Sponheim E. A randomized controlled trial of preschool-based joint attention intervention for children with autism. J Child Psychol Psychiatry 2012 Jan;53(1):97-105. PMID: 21883204.
146. Siller M, Hutman T, Sigman M. A Parent-Mediated Intervention to Increase Responsive Parental Behaviors and Child Communication in Children with ASD: A Randomized Clinical Trial. Journal of Autism and Developmental Disorders 2013;43(3):540-55. PMID: 1347458326; EJ999150.
147. Lawton K, Kasari C. Teacher-implemented joint attention intervention: pilot randomized controlled study for preschoolers with autism. J Consult Clin Psychol 2012 Aug;80(4):687-93. PMID: 22582764.
148. Murdock LC, Hobbs JQ. Picture Me Playing: Increasing Pretend Play Dialogue of Children with Autism Spectrum Disorders. Journal of Autism and Developmental Disorders 2011;41(7):870-8. PMID: 881453196; EJ928798.
149. Sofronoff K, Dark E, Stone V. Social vulnerability and bullying in children with Asperger syndrome. Autism 2011 May;15(3):355-72. PMID: 21430018.
150. Sofronoff K, Attwood T, Hinton S, et al. A randomized controlled trial of a cognitive behavioural intervention for anger management in children diagnosed with Asperger syndrome. J Autism Dev Disord 2007 Aug;37(7):1203-14. PMID: 17082978.
151. Sofronoff K, Attwood T, Hinton S. A randomised controlled trial of a CBT intervention for anxiety in children with Asperger syndrome. J Child Psychol Psychiatry 2005 Nov;46(11):1152-60. PMID: 16238662.
152. Wood JJ, Drahota A, Sze K, et al. Cognitive Behavioral Therapy for Anxiety in Children with Autism Spectrum Disorders: A Randomized, Controlled Trial. Journal of Child Psychology and Psychiatry 2009 Mar;50(3):224-34. PMID: EJ832575.
153. Wood JJ, Drahota A, Sze K, et al. Brief Report: Effects of Cognitive Behavioral Therapy on Parent-Reported Autism Symptoms in School-Age Children with High-Functioning Autism. Journal of Autism and Developmental Disorders 2009 Nov;39(11):1608-12. PMID: EJ858299.
154. Aman MG, McDougle CJ, Scahill L, et al. Medication and Parent Training in Children With Pervasive Developmental Disorders and Serious Behavior Problems: Results From a Randomized Clinical Trial. J Am Acad Child Adolesc Psychiatry 2009 Oct 23PMID: 19858761.
155. Reaven JA, Blakeley-Smith A, Nichols S, et al. Cognitive-Behavioral Group Treatment for Anxiety Symptoms in Children with High-Functioning Autism Spectrum Disorders: A Pilot Study. Focus on Autism and Other Developmental Disabilities 2009;24(1):27-37. PMID: EJ827144.

156. Sofronoff K. A Cognitive Behaviour Therapy intervention for anxiety in children with Asperger's syndrome. Good Autism Practice 2003;4:2-8.
157. Sofronoff K, Leslie A, Brown W. Parent management training and Asperger syndrome: a randomized controlled trial to evaluate a parent based intervention. Autism 2004 Sep;8(3):301-17. PMID: 15358872.
158. Chalfant AM, Rapee R, Carroll L. Treating anxiety disorders in children with high functioning autism spectrum disorders: a controlled trial. J Autism Dev Disord 2007 Nov;37(10):1842-57. PMID: 17171539.
159. Sofronoff K, Farbotko M. The effectiveness of parent management training to increase self-efficacy in parents of children with Asperger syndrome. Autism 2002 Sep;6(3):271-86. PMID: 12212918.
160. Reaven J, Blakeley-Smith A, Culhane-Shelburne K, et al. Group cognitive behavior therapy for children with high-functioning autism spectrum disorders and anxiety: a randomized trial. J Child Psychol Psychiatry 2012 Apr;53(4):410-9. PMID: 22435114.
161. Sung M, Ooi YP, Goh TJ, et al. Effects of cognitive-behavioral therapy on anxiety in children with autism spectrum disorders: a randomized controlled trial. Child Psychiatry Hum Dev 2011 Dec;42(6):634-49. PMID: 21660428.
162. Scarpa A, Reyes NM. Improving emotion regulation with CBT in young children with high functioning autism spectrum disorders: a pilot study. Behav Cogn Psychother 2011 Jul;39(4):495-500. PMID: 21457605.
163. McNally Keehn RH, Lincoln AJ, Brown MZ, et al. The Coping Cat program for children with anxiety and autism spectrum disorder: A pilot randomized controlled trial. Journal of Autism and Developmental Disorders 2013;43(1):57-67. PMID: 1312429844; 2013-00365-006.
164. Storch EA, Arnold EB, Lewin AB, et al. The effect of cognitive-behavioral therapy versus treatment as usual for anxiety in children with autism spectrum disorders: A randomized, controlled trial. Journal of the American Academy of Child & Adolescent Psychiatry 2013;52(2):132-42. PMID: 1322257699; 2013-02947-009.
165. Drahota A, Wood JJ, Sze KM, et al. Effects of cognitive behavioral therapy on daily living skills in children with high-functioning autism and concurrent anxiety disorders. J Autism Dev Disord 2011 Mar;41(3):257-65. PMID: 20508979.
166. Farmer C, Lecavalier L, Yu S, et al. Predictors and moderators of parent training efficacy in a sample of children with autism spectrum disorders and serious behavioral problems. J Autism Dev Disord 2012 Jun;42(6):1037-44. PMID: 21822762.
167. Scahill L, McDougle CJ, Aman MG, et al. Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. J Am Acad Child Adolesc Psychiatry 2012 Feb;51(2):136-46. PMID: 22265360.
168. Arnold LE, Aman MG, Li X, et al. Research units of pediatric psychopharmacology (RUPP) autism network randomized clinical trial of parent training and medication: One-year follow-Up. Journal of the American Academy of Child & Adolescent Psychiatry 2012;51(11):1173-84. PMID: 1240219479; 2012-29311-013.
169. Doyle T, Arnedillo-Sanchez I. Using Multimedia to Reveal the Hidden Code of Everyday Behaviour to Children with Autistic Spectrum Disorders (ASDs). Computers & Education 2011;56(2):357-69. PMID: 822506376; EJ904365.
170. Coben R, Padolsky I. Assessment-guided neurofeedback for autistic spectrum disorder. Journal of Neurotherapy 2007;11(1):5-23. PMID: 2007-13570-002.

171. Jarusiewicz B. Efficacy of Neurofeedback for Children in the Autistic Spectrum: A Pilot Study. Journal of Neurotherapy 2002;6(4):39-49. PMID: 2003-04346-002.
172. Adkins KW, Molloy C, Weiss SK, et al. Effects of a standardized pamphlet on insomnia in children with autism spectrum disorders. Pediatrics 2012 Nov;130 Suppl 2:S139-44. PMID: 23118244.
173. Cortesi F, Giannotti F, Sebestiani T, et al. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: A randomized placebo-controlled trial. Journal of Sleep Research 2012;21(6):700-9.
174. Kouijzer MEJ, van Schie HT, de Moor JMH, et al. Neurofeedback treatment in autism. Preliminary findings in behavioral, cognitive, and neurophysiological functioning. Research in Autism Spectrum Disorders 2010;4(3):386-99. PMID: 622182157; 2010-06408-008.
175. Manente CJ, Maraventano JC, LaRue RH, et al. Effective Behavioral Intervention for Adults on the Autism Spectrum: Best Practices in Functional Assessment and Treatment Development. Behavior Analyst Today 2010;11(1):36-48. PMID: 854555112; EJ911979.
176. Kouijzer MEJ, de Moor JMH, Gerrits BJL, et al. Neurofeedback Improves Executive Functioning in Children with Autism Spectrum Disorders. Research in Autism Spectrum Disorders 2009 Jan;3(1):145-62. PMID: EJ820617.
177. Kouijzer MEJ, de Moor JMH, Gerrits BJL, et al. Long-term effects of neurofeedback treatment in autism. Research in Autism Spectrum Disorders 2009;3(2):496-501.
178. Charlop-Christy MH, Haymes LK. Using obsessions as reinforcers with and without mild reductive procedures to decrease inappropriate behaviors of children with autism. Journal of Autism and Developmental Disorders 1996 Oct;26(5):527-46. PMID: 1996-01627-004.
179. Peters-Scheffer N, Didden R, Korzilius H, et al. A Meta-Analytic Study on the Effectiveness of Comprehensive ABA-Based Early Intervention Programs for Children with Autism Spectrum Disorders. Research in Autism Spectrum Disorders 2011;5(1):60-9. PMID: 762466213; EJ900350.
180. Kuppens S, Onghena P. Sequential Meta-Analysis to Determine the Sufficiency of Cumulative Knowledge: The Case of Early Intensive Behavioral Intervention for Children with Autism Spectrum Disorders. Research in Autism Spectrum Disorders 2012;6(1):168-76. PMID: 964176043; EJ947692.
181. Reichow B. Overview of Meta-Analyses on Early Intensive Behavioral Intervention for Young Children with Autism Spectrum Disorders. Journal of Autism and Developmental Disorders 2012;42(4):512-20. PMID: 1011396280; EJ959070.
182. Autism Speaks: State initiatives. New York: Autism Speaks. Available at: http://www.autismspeaks.org/advocacy/states.
183. Bolte EE, Diehl JJ. Measurement tools and target symptoms/skills used to assess treatment response for individuals with autism spectrum disorder. J Autism Dev Disord 2013 Nov;43(11):2491-501. PMID: 23479074.

List of Abbreviations

ABA	Applied Behavior Analysis
ABC-H	Aberrant Behavior Checklist – Hyperactivity/Noncompliance
ADI-R	Autism Diagnostic Interview - Revised
ADOS	Autism Diagnostic Observation Schedule
AEPS	Assessment Evaluation and Programming System for Infants
AHRQ	Agency for Healthcare Research and Quality
ASD	Autism Spectrum Disorder
BASC	Behavioral Assessment System for Children
CAM	Complementary and Alternative Medicine
CARS	Childhood Autism Rating Scale
CBT	Cognitive Behavioral Therapy
CER	Comparative Effectiveness Review
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
DIR	Developmental, Individual Differences, Relationship-based
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DQ	Developmental Quotient
EEG	Electroencephalogram
EIBI	Early and Intensive Behavioral Intervention
EPC	Evidence-based Practice Center
ERIC	Educational Resources Information Clearinghouse
ESDM	Early Start Denver Model
GARS	Gilliam Autism Rating Scale
HSQ	Home Situations Questionnaire
IQ	Intelligence Quotient
KQ	Key Question
JASP/ER	Joint Attention and Symbolic Play/Engagement and Regulation Intervention
LEAP	Learning Experiences and Alternative Program for Preschoolers
M-CHAT	Modified Checklist for Autism in Toddlers
NR	Not Reported
nRCT	Non-Randomized Controlled Trial
NS	Not Statistically Significant
PARS	Pediatric Anxiety Rating Scale
PDD-NOS	Pervasive Developmental Disorder- Not Otherwise Specified
PECS	Picture Exchange Communication System
PEER	Peer-Mediated Social Skills Training
PICOS	Population, Intervention, Comparator, Outcomes, Timing, and Setting
RCT	Randomized, Controlled Trials
SCARED	Screen for Childhood Anxiety Related Emotional Disorders
SDARI	Sociodramatic Affective Relational Intervention
SS GRIN-HFA	Social Skills Group Intervention – High Functioning Autism
TEP	Technical Expert Panel
TOO	Task Order Officer
TEACCH	Treatment and Education of Autistic and Related Communication Handicapped Children
UCLA	University of California, Los Angeles