

Draft Comparative Effectiveness Review

Number XX

Comparative Effectiveness of Interventions for Adolescents and Young Adults with Autism Spectrum Disorders

Prepared for:

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Contract No. <redacted>

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AHRQ Publication No. xx-EHCxxx
<Month Year>

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Author I, Author II. Comparative Effectiveness of <Title>. Comparative Effectiveness Review No. xx. (Prepared by the <Name> Evidence-based Practice Center under Contract No. xxx-xx-xxxx.) AHRQ Publication No. xx-EHCxxx. Rockville, MD: Agency for Healthcare Research and Quality. <Month Year>. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

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

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

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

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

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

We welcome comments on this CER. 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 e-mail to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

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Comparative Effectiveness of Interventions for Adolescents and Young Adults with Autism Spectrum Disorders

Structured Abstract

Objectives. We systematically reviewed evidence on therapies for adolescents and young adults (ages 13 to 30) with autism spectrum disorders (ASD). We focused on the outcomes, including harms and adverse effects, of interventions addressing the core symptoms of ASD; common medical and mental health comorbidities occurring with ASD; the attainment of goals toward functional/adult independence; educational and occupational/vocational attainment; quality of life; access to health and other services; and the transitioning process (i.e., process of transitioning to greater independent functioning). We also addressed the effects of interventions on family outcomes including parent distress and satisfaction with interventions.

Data sources. We searched MEDLINE® via PubMed, PsycInfo®, the Educational Resources Information Clearinghouse, and the Cumulative Index of Nursing and Allied Health Literature databases as well as the reference lists of included studies.

Review Methods: We included studies published in English from January 1980 to May 2011. We excluded intervention studies with fewer than 20 adolescents or young adults with ASD or fewer than 20 parents or family members of such individuals and studies lacking relevance to ASD treatment.

Results: We identified 31 unique studies, most of which were poor quality. Five studies, mostly of medical interventions, were fair quality, and none was good. In the behavioral literature, studies of group- and computer-based interventions reported short-term gains in social skills. Two poor quality studies of educational interventions reported some gains in vocabulary and reading. Five small studies investigated disparate interventions addressing highly specific adaptive/life skills with some positive results in studies typically of short duration. Studies of vocational interventions, all of poor quality, suggested that on-the-job supports may promote employment in the community, which may be related to improving quality of life and cognitive performance. Little evidence supports the use of medical interventions in adolescents and young adults with ASD; however, antipsychotic medications and serotonin reuptake inhibitors were associated with improvements in specific challenging behaviors. Similarly, little evidence supports the use of allied health interventions including facilitated communication.

Conclusions: Few studies target empirical investigation of treatment approaches for adolescents and young adults with ASD, and as such there is very little evidence for specific treatment approaches in this population; this lack of studies is especially prominent for evidence-based approaches to support the transition of youth with autism to adulthood. Most of the studies identified were of poor quality, which may reflect the relative recency of the field. A small number of studies, primarily of medical interventions, had fair quality. Behavioral, educational, and adaptive/life skills studies were typically small and short-term and suggested some potential

improvements in social skills and functional behavior. Small studies suggested that vocational programs may increase employment success for some individuals. Little evidence supports the use of medical or allied health interventions in the adolescent and young adult population. The medical studies that have been conducted focused on the use of medications to address specific challenging behaviors, including irritability and aggression, for which effectiveness in this age group is largely unknown and inferred from studies of young children.

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Effective Health Care

Comparative Effectiveness of Interventions for Adolescents and Young Adults with Autism Spectrum Disorders

Executive Summary

Effective Health Care Program

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Autism Spectrum Disorders (ASD) are among the most common neurodevelopmental disorders, with an estimated prevalence of one in 110 children in the United States having an ASD.¹ They are typically diagnosed in early childhood, often at or before preschool age. The diagnosis is fundamentally behaviorally based (i.e., there is no specific genetic test or clinical/laboratory procedure for diagnosis) and rests on documented core impairments related to social interaction, communication, as well as restricted and repetitive behavior.

Diagnoses made by clinical providers, often pediatricians or behavioral providers, are based on documented symptom patterns in these domains. Numerous screening and diagnostic tools are available to help document and measure symptoms of autism, with research investigations increasingly utilizing such measures in combination with clinical diagnoses in order to more accurately describe, measure, and analyze the heterogeneity in presentation associated with ASD. In addition to impairments in core symptom areas, many individuals with ASD also have impaired cognitive skills, atypical sensory behaviors, or other complex medical and psychiatric symptoms and conditions, such as seizure disorders, hyperactivity, anxiety, and self-injury/aggression.

More than 55,000 individuals between the ages of 15 and 17 in the United States likely have an ASD.² For some individuals, core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and over time;³⁻⁵ however, some degree of impairment typically remains throughout the lifespan.⁶ As children transition to adolescence and young adulthood, developmentally appropriate interventions to ameliorate core deficits may continue, but the focus of treatment often shifts toward promoting adaptive behaviors that can facilitate and enhance independent

functioning.⁶ Treatments for some must take into account new emergent symptoms as well as engagement with new developmental challenges (e.g., independent living, vocational engagement, post-secondary education).

There is also evidence to suggest that improvements in symptoms and improvements in problem behaviors may slow down or stop after youth with ASD leave high school.⁷ This change in improvement is likely due, at least in part, to the termination of services received through the secondary school system upon high school exit, as well as the lack of adult services and long waiting lists for many services.^{7,8} This issue of the lack of services available to help young adults with ASD transition to greater independence has been noted by researchers for a number of years and is increasingly a topic in the lay media.⁹

Interventions Used to Treat ASD

Individuals with ASD have significant impairments in social interaction, communication, and repetitive behavior. In addition to impairments in these core areas, some people with ASD also have impaired cognitive skills, atypical sensory behaviors, or other complex medical and psychiatric symptoms and conditions, such as seizure disorders, hyperactivity, anxiety, and self-injury/aggression. The expression and severity of ASD symptoms differ widely across individuals and over time. Treatments may include a range of behavioral, psychosocial, educational, medical, and complementary approaches focused on transitional process and improving outcomes for parents/families of individuals with ASD during adolescence and adulthood.

ASD in Adolescence and Young Adulthood

Current data suggest that attainment of independent living or employment in adulthood for individuals with an ASD is variable, with factors that predict the ability to live and work independently not well elucidated.⁶ Research conducted to date has suggested that most individuals with ASD will require some sort of intervention, often at very intensive levels, throughout adolescence and adulthood, and the estimated costs of medical and non-medical care (e.g., special education, daycare) are prodigiously 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 at \$3.2 million and at about \$35 billion for an entire birth cohort of individuals with autism.¹⁰ A study of health care utilization in a large group health plan revealed increased medication costs in older children with an ASD when compared with younger children, as well as similarly aged adolescents without an ASD; other care costs were also higher in this population, including a significantly increased rate of hospitalizations.¹¹

Costs of transitional and employment programs are also high for young adults with ASD. A recent analysis of U.S. Federal- and State-funded vocational rehabilitation programs showed that enrolled individuals with ASD were among the most costly of nine disability groups examined, with costs even higher among those with ASD and another comorbid disability. These data also showed, however, that those with ASD had a higher rate of employment (40.8 percent) at the time of case closure when compared with those with other disabilities, though with fewer work hours and lower wages than some other disability groups.¹² One study reported an average expenditure for purchased vocational rehabilitation services of \$3,342 ± \$5,662 in 2005.¹³

There is no cure for ASD and currently no global consensus regarding 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

core ASD features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. Investigators have noted that less data on therapies for adolescents or young adults exist than for younger children,¹⁴ and such research is increasingly important as the prevalence of ASD continues to grow and as children with ASD diagnoses reach adolescence.

Objectives

The goal of this review is to examine the effects of available interventions among adolescents and young adults with ASD, focusing on the following outcomes: core symptoms of ASD (impairments in social interaction, communication, and repetitive behavior); medical and mental health comorbidities; functional behaviors and independence; the transition to adulthood, and family outcomes.

Population

We focused this review on therapies for adolescents and young adults (ages 13 to 30) with ASD as well as interventions aimed at family members of such individuals.

Interventions

Studies assessed interventions falling into the broad categories of behavioral, educational, adaptive/life skills, vocational, medical, and allied health approaches.

Comparators

Comparators included no treatment, placebo, and comparative interventions or combinations of interventions.

Outcomes

Intermediate outcomes included changes in core ASD symptoms and in common medical and mental health comorbidities as well as effects on functional behavior, the transition process, and family outcomes. Long term outcomes included changes in adaptive/functional independence, academic and occupational attainment or engagement, psychological well-being, and psychosocial adaptation. We also assessed the harms of interventions, defined by the Evidence based Practice Center Program as all possible adverse consequences of an intervention, including adverse events (Figure ES-1).¹⁵

Key Questions

We have synthesized evidence in the published literature to address these key questions:

Key Question 1: Among adolescents and young adults with ASD, what are the effects of available interventions on the core symptoms of ASD?

Key Question 2: Among adolescents and young adults with ASD, what are the effects of available interventions on common medical and mental health comorbidities (e.g., epilepsy, sleep disorders, motor impairments, obesity, depression, anxiety, acute and episodic aggression, attention deficit hyperactivity disorder, etc.)?

Key Question 3: Among adolescents and young adults with ASD, what are the effects of available interventions on functional behavior, attainment of goals toward independence, educational attainment, occupational/vocational attainment, life satisfaction, access to health and other services, legal outcomes, and social outcomes?

Key Question 4: Among adolescents and young adults with ASD, what is the effectiveness of interventions designed to support the transitioning process, specifically to affect attainment of goals toward independence, educational attainment, occupational/vocational attainment, life satisfaction, access to health and other services, legal outcomes, and social outcomes?

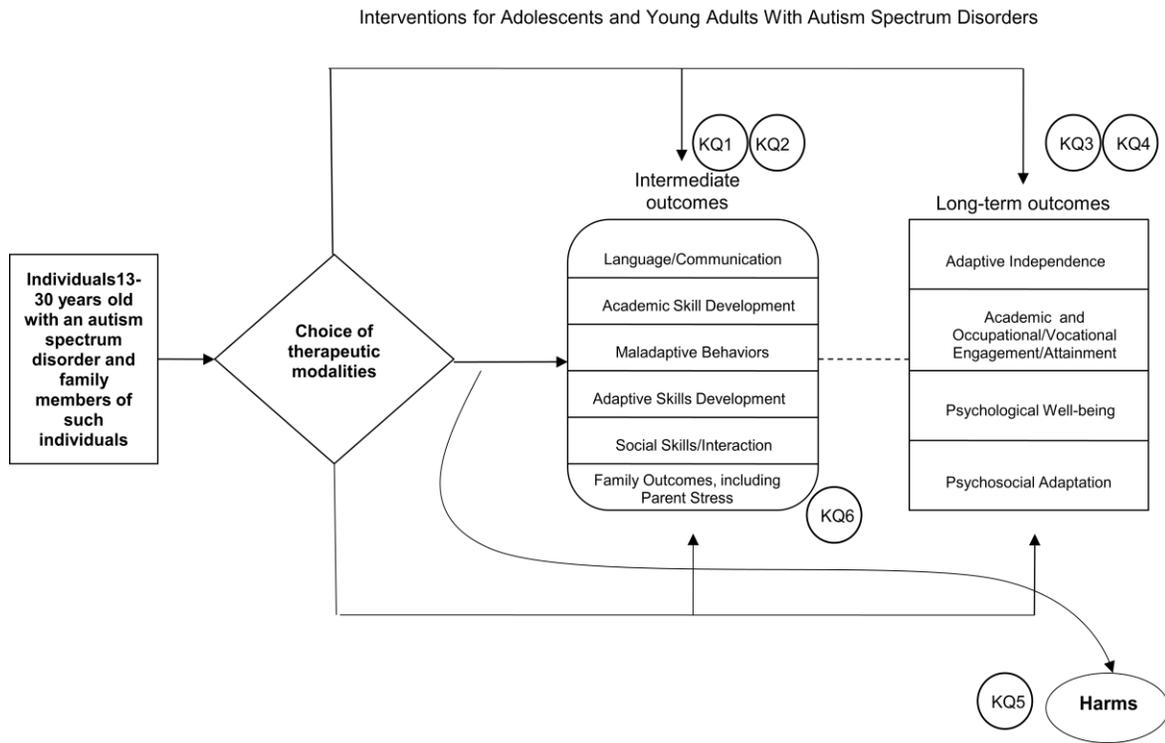
Key Question 5: Among adolescents and young adults with ASD, what harms are associated with available interventions?

Key Question 6: What are the effects of interventions on family outcomes?

Analytic Framework

We initially developed the analytic framework (Figure ES-1) based on clinical and research expertise and with input from a focus group of parents of adolescents and young adults with ASD. We then refined it with input from our key informants and Technical Expert Panel (TEP) members. The framework summarizes the process by which individuals with ASD and their families/caregivers make and modify treatment choices. Treatment choices may target intermediate outcomes including changes in communication skills, academic skill development, or social skills. Interventions lead to long-term outcomes such as adaptive independence and changes in psychosocial well-being. Family outcomes such as parent distress may also be targeted by interventions and may lead in turn to long-term outcomes. Finally, interventions may be associated with harms/adverse effects. Numbers in circles within the diagram indicate the placement of key questions in relation to the treatment process.

Figure ES-1. Analytic Framework for Interventions for Adolescents and Young Adults with ASD



Note: ASD=autism spectrum disorders; KQ=Key Question.

Methods

Input from Stakeholders

The topic was nominated in a public process. With parent focus group and key informant input, we drafted initial key questions, which were reviewed by the Agency for Healthcare Research and Quality (AHRQ) and posted to a public website for public comment. Using public input, we drafted final key questions, which were reviewed by AHRQ. We convened a TEP to provide input during the project on issues such as setting inclusion/exclusion criteria and assessing study quality. In addition, the draft report was peer reviewed and available for public comment.

Data Sources and Selection

Data Sources

We searched 4 databases: MEDLINE® via the PubMed interface, PsycINFO (psychology and psychiatry literature), the Educational Resources Information Clearinghouse, and the Cumulative Index of Nursing and Allied Health Literature database. We used a combination of controlled vocabulary terms appropriate for each database (e.g., MEDLINE vocabulary term autistic disorder) and keywords related to ASD (e.g., Asperger syndrome). Appendix A of the full report details each search strategy. We hand searched reference lists of included articles and

recent reviews for additional studies. 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 included all study designs except single case reports provided that studies reported on an intervention aimed at individuals with ASD between the ages of 13 and 30 or family members of such individuals. We excluded studies that:

- Were not original research
- Did not report information pertinent to the key questions
- Did not address treatment modalities aimed at core symptoms of ASD, common comorbidities, functional/life skills outcomes, family-related outcomes, or assisting with the transition to adulthood
- Did not include aggregate data (i.e., included only individual data for each participant) or data presented only in graphics/figures
- Were single case reports
- Were not published in English
- Were published before 1980 and the publication of autism diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Third edition*.

We also excluded studies that included fewer than 20 total participants in the target age range with ASD or family members of such individuals. Our goal was to identify and review the best evidence for assessing the efficacy and effectiveness of therapies for adolescents and young adults with ASD, with an eye toward utility in the treatment setting.

Interventions to address ASDs 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 20 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. The minimum sample size of 20 allowed us 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.

Screening of Studies

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

Data Extraction and Quality Assessment

Data Extraction

All team members entered information into the evidence tables. After initial data extraction, a second team member edited entries for accuracy, completeness, and consistency. In addition to outcomes for treatment effectiveness and family outcomes, we extracted data on harms/adverse effects.

Quality Assessment

Two reviewers independently assessed quality (study design, diagnostic approach, participant ascertainment, intervention characteristics, outcomes measurement, and statistical analysis) using a quality assessment methodology adapted from that used in a prior AHRQ review of therapies for children with ASD.¹⁶ We resolved differences through discussion, review of the publications, and consensus with the team. We rated studies as good, fair, or poor quality and retained poor studies as part of the evidence base discussed in this review. More information about our quality assessment methods is in the full report, and Table ES-1 describes the quality ratings.

Table ES-1. 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.

Data Synthesis and Analysis

Evidence Synthesis

We used summary tables to synthesize studies and summarized the results qualitatively.

Strength of the Evidence

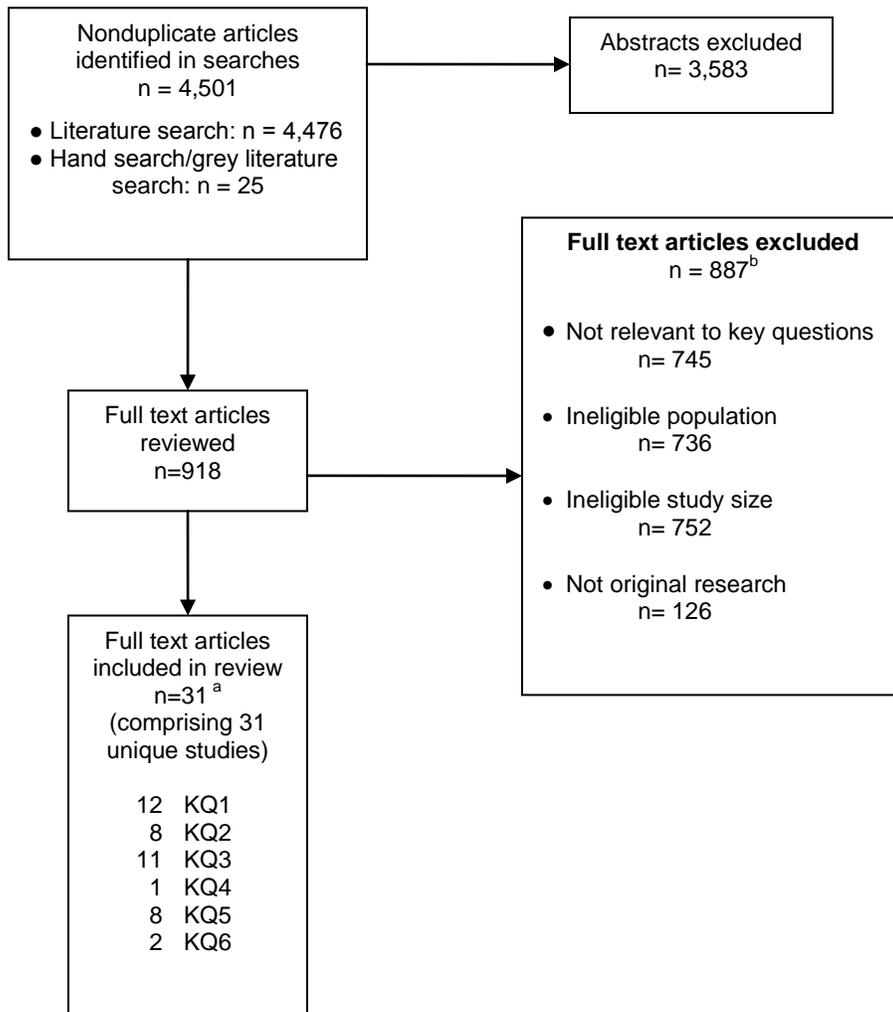
The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence. Strength of evidence can be regarded as insufficient, low, moderate, or high. It describes the adequacy of the current research, in quantity and quality, and the degree to which the entire body of current research provides a consistent and precise estimate of effect. We established methods for assessing the strength of evidence based on the Evidence-based Practice Centers’ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.¹⁷

Results

Article Selection

Of the entire group of 4,501 citations, 918 articles required full text review (Figure ES-2). Of the 918 full text articles reviewed, we retained 31 papers (comprising 31 unique studies) and excluded 887 papers.

Figure ES-2. Disposition of studies identified for this review



^aOne paper¹⁸ reports two unique studies

^bNumbers do not tally as studies could be excluded for multiple reasons
KQ=key question; n=number.

Organization of Results

As noted, we classified studies by broad category of intervention (behavioral, educational, vocational, adaptive/life skills, medical, and allied health). With the exceptions of studies of medical and vocational interventions, which included at least two studies addressing the same intervention, the other categories of interventions largely comprised single studies of unique interventions. Most studies (n=12) also targeted core symptoms of ASD (Key Question 1) or functional behavior/independent living skills (n=11) (Key Question 3). Eight studies examined comorbidities (defined broadly to encompass associated symptoms such as irritability) commonly occurring with ASD (Key Question 2).

One study addressed interventions targeting the transition process (Key Question 4), eight studies of medical interventions addressed harms (Key Question 5), and two studies assessed effects of an intervention on family outcomes (Key Question 6). Because questions were addressed by a number of small, single studies of a given intervention, we discuss all studies together in the following sections instead of divided by key question. This approach allows us to present the findings of this disparate literature more clearly.

Across all categories of interventions, most studies (n=26) were of poor quality, and none was good quality. Five RCTs were fair quality: four that investigated pharmacologic agents¹⁹⁻²² and one allied health study that assessed a leisure/recreation program.²³ Given the small number of studies and generally poor quality, we considered the strength of the evidence for all interventions addressing all outcomes as insufficient.

Studies of Behavioral Interventions

We identified six studies^{18, 24-27} of behavioral interventions. One paper¹⁸ reports two unique studies. Studies were conducted in the United States, Europe, and Canada and included a total of 246 participants. Five studies (with two unique studies reported in one paper¹⁸) examined group- or computer-based social skills interventions^{18, 24-26} and an additional study assessed an intensive behavioral treatment provided at a semi-residential facility.²⁷ All studies were of poor quality. Studies assessing social skills approaches reported some benefits in emotion recognition and participation in social activity over the short term.^{18, 24-26} The study of an intensive approach reported modest improvements in adaptive behavior over a 2 year period.²⁷ This study also assessed parental satisfaction with treatment, noting high levels of satisfaction overall.

Studies of Educational Interventions

Two studies, both poor quality, examined educational interventions.^{28, 29} Studies were conducted in the United States and Canada and included fewer than 50 total individuals with ASD. In one study, individuals with ASD and mean mental age scores of 3.3 years received language instruction using 2 teaching methods, with no significant difference observed between methods.²⁸ In a randomized study assessing strategies to promote reading comprehension²⁹ scores generally improved overall.

Studies of Adaptive/Life Skills Interventions

We identified five studies, all of poor quality, of interventions focused on adaptive behavior.³⁰⁻³⁴ Treatment duration varied tremendously from a day-long experiment to a study examining outcomes across a 2 year interval in a residential facility. Overall these studies included a total of 191 individuals with ASD. All studies were conducted in the United States, and at least three explicitly included participants with intellectual disability.^{30, 32, 33} Across studies, participants made very specific short-term gains in learning or successfully executing an adaptive or life skills-focused task, including lacing shoes, exiting a building in response to an alarm, or using a personal digital assistant to help with remembering activities. In one study of a residential facility employing a Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH)-based model, exploratory analyses showed variable results with few significant changes in skills or negative behaviors over time across individuals in the TEACCH program or in institutions, family homes, or group homes.³⁰ Parents were significantly more satisfied with the TEACCH program overall.

A final poor quality case series addressed the transitioning process by assessing effects related to implementing a classroom process—changing rooms throughout the school day—that individuals would likely encounter as they move to high school or college; the study reported no increase in disruptive behavior after the implementation of classroom rotation.³⁴

Studies of Vocational Interventions

We identified six papers from five unique study populations that addressed the impact of supported employment/vocational interventions.^{8, 13, 35-38} Studies were conducted in the United States and Europe and included over 1,900 individuals with ASD; roughly 1,700 of these were included in an administrative database study assessing use of vocational rehabilitation services. All studies were considered poor quality. Interventions all involved finding and implementing on-the-job supports (broadly defined as services to promote job placement and job retention) for young adults with ASD. In studies comparing supported employment in the community to sheltered workshops, participants in supported employment groups experienced reductions in autism symptoms and improvements in measures of cognition and quality of life.³⁵⁻³⁷

In long term studies of a job finding program in the UK,^{8, 38} young adults in a supported employment group were significantly more likely to find paid employment than those in the control group (63.3 percent vs. 25 percent), with the majority of those employed showing job satisfaction. One final study identified individuals with ASD in a U.S. vocational rehabilitation dataset. These data illustrated that the presence of on-the-job supports was related to a higher likelihood of employment in the community (competitive or supported).¹³

Studies of Medical Interventions

Eight studies of pharmacologic agents, four of fair¹⁹⁻²² and four of poor quality,³⁹⁻⁴² met our review criteria. The studies included a total of 272 individuals with ASD, and all were conducted in the United States, Canada, or Europe in academic clinics. All studies were funded using institutional and grant sources. Three randomized controlled trials (RCTs), one fair quality²² and two poor,^{21, 39} addressed the efficacy of antipsychotic medications including risperidone and haloperidol. One fair quality RCT investigated the opiate antagonist naltrexone.²⁰ Of five studies examining serotonin reuptake inhibitors (SRIs),^{19, 21, 40-42} two RCTs were fair quality,^{19, 21} and three case series were poor.⁴⁰⁻⁴²

All studies of medical interventions addressed outcomes related to comorbid conditions such as irritability or harms of treatments. Studies of antipsychotic medications reported some reductions in repetitive behavior, aggression, hyperactivity, and irritability in treatment groups over time periods of 7 to 24 weeks. Brief treatment with naltrexone (4 weeks) was associated with increases in stereotypy (repetitive or ritualistic behavior or movement) in the treated group. Studies of SRIs reported some improvements in treated participants in measures of irritability, repetitive behavior, and aggression over treatment durations of 7 to 12 weeks. One longer term case series reported improvements in general symptom severity and compulsive behavior in individuals receiving fluoxetine for a mean of 6 months.⁴²

All medical studies reported harms of treatment. Harms or adverse effects reported in studies of antipsychotic medications included sedation, gastrointestinal complaints, weight gain, increased appetite, fatigue, dystonia, and depression.^{22, 39, 43} Adverse effects described in the study of naltrexone included nausea, fatigue, sedation, and an increase in self-injurious behavior and stereotypy.²⁰ Harms noted in studies of SRIs included fatigue, tremor, tachycardia, agitation, gastrointestinal complaints, sedation, anxiety, agitation, and insomnia.^{19, 21, 40-42}

Studies of Allied Health Interventions

We identified five studies of allied health interventions^{23, 44-47} including one fair quality RCT investigating a leisure/recreation program,²³ two poor quality case series addressing music therapy,^{46, 47} and two poor case series addressing facilitated communication.^{44, 45} Studies included a total of 174 individuals with ASD, and the duration of treatment ranged from 20 hours to 12 months in four studies;^{23, 44, 45, 47} one study of music therapy reviewed data from participants who had participated in varying hours of therapy.⁴⁶ Studies of music therapy reported some improvements in social skills using unvalidated measures.^{46, 47} Studies assessing facilitated communication noted little communication improvement associated with facilitation and some evidence of facilitator influence on participants' responses.^{44, 45} The study examining a recreation program reported improvements in stress-related scores for individuals in the intervention group compared with those in the control group ($p < 0.001$). Overall quality of life scores similarly improved for intervention participants compared with the control group.²³

Discussion

Key Findings

Despite a growing population of adolescents and young adults who have diagnoses of an ASD, there is very little high quality research available to help understand the impact of specific intervention approaches for individuals with ASD. Research to date is scarce, and what is available is lacking in scientific rigor and limited in terms of guiding clinical practice. We identified a total of 31 studies (one paper reported two separate studies), of which ten were randomized controlled trials. Although RCTs are often considered the gold standard for assessing intervention effectiveness, particularly in a complex behavioral field with merging research such as this, observational designs can be rich sources of information. Nonetheless, most studies were of poor quality; only five were fair quality and none were good quality. The strength of the evidence (degree of confidence that the observed effect of an intervention is unlikely to change) across all interventions and outcomes was insufficient.

In the behavioral literature research, social skills interventions utilizing group^{24, 25} and computer-based interventions^{18, 26} suggested improvements across a variety of caregiver reported social skills and emotion recognition capacities respectively. However, each study employed a different approach and paradigm, making comparison across interventions impossible. Likewise, such social skills interventions have yet to demonstrate consistent generalization of skills across settings and often limit interventions to individuals with average to above average verbal and/or cognitive abilities.

Only a single poor quality case series examined the effects of a more intensive, comprehensive intervention approach. This study suggested improvement in adaptive skills and high levels of family satisfaction with services for 34 adolescents receiving treatment in a residential treatment setting over the course of two years. Given the lack of adequate comparison group in this setting, there is very little information surrounding the impact of comprehensive behavioral intervention approaches for this population.

Research into educational approaches for adolescents and young adults with ASD is very limited, with only two small crossover studies identified in this population. These studies^{28, 29} focused on the impact of highly specified educational strategies and outcomes (e.g. vocabulary

development) and ultimately provide little evidence to support selection of either specific or various broad-based educational strategies.

Studies of adaptive/life skills-focused interventions meeting our criteria were of poor quality, addressed disparate interventions, and included few participants. No study included more than 36 individuals with ASD, and most had concomitant intellectual disability. Studies documented highly specified short term gains in learning or successfully executing an adaptive or life skills-focused tasks, but the applicability and generalization of these findings is limited by the highly specified approaches utilized³⁰⁻³⁴ Additionally, studies were typically uncontrolled and of short duration.

Among five studies focused on supported employment/vocational interventions,^{8, 13, 35-38} all focused on on-the-job supports as the employment/vocational intervention. No other vocational interventions were reported in the literature meeting our study criteria. Our ability to know the ultimate benefit of supported employment programs is limited given the existing research. No study utilized random assignment, making it difficult to draw conclusions about the effectiveness of the programs. Regardless, the clearest benefit of supported employment interventions appears to be in increasing rates of employment for young adults with ASD, with three of the studies focused on employment as the outcome of interest.^{8, 13, 38} There is less evidence of the importance of supported employment interventions in other domains, with single studies reporting that supported employment was associated with improvements in quality of life,³⁶ cognitive functioning,³⁵ or improved core symptoms,³⁷ relative to young adults with ASD in sheltered work settings.

Supported employment interventions remain understudied. For example, only one study examined rates of employment for programs that lasted 3 years or longer.⁸ Further, this longer-term study did not include a control group, making it impossible to determine the rates of employment over time for young adults with ASD who were not participating in the supported employment intervention. Finally, none of the studies examined whether increased employment rates or improvements in other outcomes were sustained after the termination of the supported employment intervention.

The use of medical interventions in adolescents and young adults with ASD is common.⁴⁸ However, there is little evidence that supports the use of medical interventions specifically in this population. Overall, most studies focused on the use of medications to address specific challenging behaviors (i.e., aggression or irritability). Four studies were fair quality,¹⁹⁻²² and five were poor.^{39-42, 44} The most consistent findings were identified for antipsychotic medications. A fair quality RCT studying risperidone found improvements in aggression, repetitive behavior, sensory motor behaviors, and overall behavioral symptoms.²² A cross-over study of risperidone also showed a significant reduction of irritability/agitation ratings with risperidone treatment, but the control was indirect.³⁹ A placebo-controlled cross-over study found that haloperidol significantly improved hyperactivity/defiance ratings, but no significant difference was found for irritability/agitation or other symptoms.²¹ While limited literature supports the use of risperidone in adolescents or young adults with ASD, the efficacy of risperidone in children has moderate strength of evidence⁴⁹ that is consistent with the results of the one fair RCT and one poor cross-over study in adults with ASD. There is therefore no evidence to suggest that the effects of risperidone for irritability/agitation in ASD are specific to a particular age range.

A number of studies of SRIs were identified but with little consistency across studies. An RCT of fluvoxamine showed decreases in repetitive behavior, aggression, autistic symptoms, and language usage.¹⁹ In contrast, no significant differences were observed in a cross-over study of

clomipramine versus placebo.²¹ Three case series of SRIs were also identified, including sertraline, fluoxetine, and clomipramine, with each study reporting some benefit to treatment.⁴⁰⁻⁴² A cross-over study of the opioid receptor antagonist naltrexone found no significant improvements in problem behavior and showed worsening of stereotyped behavior with naltrexone treatment compared to placebo.²⁰

Based upon the published studies in adolescents and adults with ASD, the strength of evidence is insufficient for harms associated with medications tested in this population. As in the case of efficacy, the data on adverse effects associated with risperidone, including sedation and weight gain, are consistent with the strong strength of evidence for these adverse effects in children with ASD.⁴⁹ There is therefore no evidence to suggest that the adverse effects of risperidone in ASD are limited to a particular age range. Of course, this does not mean that other medications tested in ASD are free of adverse effects. It is reasonable to expect that, in contrast to efficacy, which is more likely to be specific to disorder and symptom, adverse effects are more likely to extend across diverse groups of subjects studied. Clinicians evaluating the evidence and sharing information with families routinely take this perspective, as does the Food and Drug Administration in mandating that all adverse events be listed for a drug, rather than just those for a particular indication.

Few studies of allied health interventions met our criteria.⁴⁴⁻⁴⁶ One fair quality RCT assessed a 12-month recreation program²³ and reported improved quality of life and lower stress scores in individuals participating in the leisure/recreation program compared with those on a waiting list. Two studies of facilitated communication used approaches designed to assess the effects of facilitation both with and without facilitators' awareness of the word being prompted. Both studies demonstrated some facilitator influence without specific effects on participants' independent ability to communicate. One retrospective study of a music therapy program reported some positive effects on participants' social skills using largely subjective outcome measures.⁴⁶ One poor quality case series⁴⁷ included 22 young adults engaged in a music therapy intervention. Nearly all participants reported making friends during the program and were generally satisfied with the program. Both studies assessed outcomes shortly after treatment, so longer-term effects of the interventions are not known.

Applicability of the Evidence

Study populations across interventions were highly variable. A number of studies included individuals with ASD and significant intellectual disability or language impairment, while studies assessing vocational and social skills-related behavioral interventions typically included higher functioning individuals. Studies of medical interventions were all conducted in academic clinic settings, which may limit applicability to the general population. Given the variability and typically limited information concerning developmental, cognitive, and behavioral characteristics of study populations, it is unclear how findings might apply across varying individuals with ASD.

Future Research

The period of development representing the transition from adolescence to early adulthood presents numerous challenges for individuals with and without neurodevelopmental challenges. These challenges are compounded for individuals with ASD as they are presented with additional complexities requiring efforts to maximize the possibility of a positive transition and achievement of individual goals for independence. Despite increasing numbers of adolescents

facing the transition from adolescence to adulthood, intervention research lags behind. To date, there is not sufficient strength of evidence for documenting the effects of any interventions in this age group on specific outcomes.

Overall, there is a dearth of evidence in all areas of care for adolescents and young adults with autism spectrum disorders and it is urgent that more rigorous studies be developed and conducted. The lack of randomized, controlled trials is notable in all categories of intervention, but especially so in medical interventions, where substantial adverse events may be associated with medication use in adolescence. Only three studies^{8, 30, 36} reported more than 12 months of followup; longer term data are needed in all areas of therapy.

The behavioral literature generally focuses on a subset of individuals with ASD; often those who are higher functioning, and may not be representative of the range of individuals with ASDs. In particular, more attention is warranted to understand the impact of behavioral interventions in the lives of individuals and how these interventions generalize to real-world impact and outcome.

Few studies addressing educational interventions in the adolescent and young adult population have been conducted, and studies focusing on life skills or adaptive behaviors have included few individuals in typically short-term studies focused on highly specific short-term intermediate outcomes. More research in both areas and over broader timeframes with more clearly defined populations is critical for helping individuals with ASD transition to greater independence.

In vocational research, studies are needed that illuminate which aspects of multifaceted supported employment programs have the greatest impact. Studies that do show evidence of effectiveness in this area should collect longer-term data to describe the degree to which findings, including the duration of employment, continue after the intervention itself is removed. These studies should also broaden the outcomes measured, to include other functional outcomes such as quality of life, educational attainment, residential outcomes and social outcomes. Similarly, allied health studies are needed to understand best approaches to fostering independent living skills.

Medical studies conducted in adolescents and young adults have focused largely on problem behaviors. Clear evidence supports the use of risperidone and aripiprazole in children with ASD.⁴⁹ The only fair quality study of risperidone in adults is consistent with the findings in children, but the strength of evidence based upon the adult literature alone is insufficient to draw firm conclusions. Population studies may be helpful to empirically group ASD patients by age in a way that fosters more effective studies of treatments. Understanding the age-appropriateness of potential medical treatments as based on social, physiological, pharmacological, and functional characteristics of the population would help to prioritize future research. Increased use of such standardized age groupings would facilitate comparisons of effectiveness within medical intervention categories as well as with non-medical therapies.

Thus far, medication research in adolescents and young adults with ASD has been limited to compounds that are already approved for other indications. As targeted treatments for ASD emerge, initial studies will need to study adult populations to establish safety before moving into studies of adolescents and finally children. It will be critical to consider the appropriate outcome measures and settings in which to study medication response in adults. The heterogeneity in settings for adults with ASD is a significant impediment to assessing symptom response. Ideally, medications would be combined with an educational or psychosocial intervention that would mirror the school and therapeutic settings in which children with ASD show improvements in

social, communication, or behavioral function. Without some level of educational or social challenge, it may be quite difficult to assess medication response.

Research is needed on which outcomes to use in future studies. The Aberrant Behavior Checklist is the best outcome measure for behavioral symptoms in ASD in terms of both validity and reliability, but it does not directly index anxiety, mood, social, or communication function nor does it capture broader outcomes such as quality of life. More outcome measures are needed to allow assessment of a broader range of symptoms, particularly in individuals who may be higher functioning. No studies provide adequate information on longer-term outcomes, and particularly on outcomes related to achieving goals for independence. To some degree, this reflects a lack of understanding and consensus about optimal outcomes and how to measure them.

Research is also necessary to understand how individuals' expression of ASD symptoms and the severity of symptoms may affect treatment over the lifespan. Foundational research is necessary to understand the goals of individuals with autism and their families as future research studies are planned. Similarly, little research addressing the effects of family and caregiver interactions and characteristics on the responses of individuals' with ASD to interventions exists.

Conclusions

Given the number of individuals affected by ASD, there is a dramatic lack of evidence on best approaches to therapies for adolescents and young adults with these conditions. In particular, families have little in the way of evidence-based approaches to support interventions capable of optimizing the transition of teens with autism into adulthood. Most of the studies identified were of poor quality; while the fair quality studies were primarily of medical interventions. Behavioral, educational, and adaptive/life skills studies were typically small and short term and suggested some improvements in social skills and functional behavior.

Individual studies also suggested that vocational programs may increase employment success, but the studies were small. By the same token, little evidence supports the use of medical or allied health interventions in the adolescent and young adult population. Although the studies that have been conducted focused on the use of medications to address specific challenging behaviors, the effectiveness in managing irritability and aggression in this age group remains largely unknown and can at best be inferred from studies of young children.

Internet Citation

{Provided by AHRQ} Authoring EPC, Title, Comparative Effectiveness Review: Number ##. AHRQ Publication Number No. 0#-###, Month 200#. Agency for Healthcare Research and Quality, Rockville, MD. <http://www.effectivehealthcare.ahrq.gov/xxxxxxx>

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Evidence Report

Introduction

Need for Evidence Regarding Treatment of Autism Spectrum Disorders in Adolescents and Young Adults

Autism Spectrum Disorders (ASD) are among the most common neurodevelopmental disorders, with an estimated prevalence of one in 110 children in the United States having an ASD.¹ They are typically diagnosed in early childhood, often at or before preschool age. The diagnosis is fundamentally behaviorally based (i.e., there is no specific genetic test or clinical/laboratory procedure for diagnosis) and rests on documented core impairments related to social interaction, communication, as well as restricted and repetitive behavior. Diagnoses made by clinical providers, often pediatricians or behavioral providers, are based on documented symptom patterns in these domains.

Numerous screening and diagnostic tools are available to help document and measure symptoms of autism, with research investigations increasingly utilizing such measures in combination with clinical diagnoses in order to more accurately describe, measure, and analyze the heterogeneity in presentation associated with ASD. In addition to impairments in core symptom areas, many individuals with ASD also have impaired cognitive skills, atypical sensory behaviors, or other complex medical and psychiatric symptoms and conditions, such as seizure disorders, hyperactivity, anxiety, and self-injury/aggression.

More than 55,000 individuals between the ages of 15 and 17 in the United States likely have an ASD.² For some individuals, core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and over time;³⁻⁵ however, deficits typically remain throughout the lifespan although developmental expression may vary.⁶ As children transition to adolescence and young adulthood, developmentally appropriate interventions to ameliorate core deficits may continue, but the focus of treatment often shifts toward promoting adaptive behaviors that can facilitate and enhance independent functioning.⁶ Treatments for some must take into account that new symptoms may emerge with adolescence as well as engagement with new developmental challenges (e.g., independent living, vocational engagement, post-secondary education). In particular, families and caregivers have to make choices regarding care that cross a broad spectrum of clinical, behavioral and educational areas.

Current data suggest that attainment of independent living or employment in adulthood for individuals with an ASD is variable, with factors that predict the ability to live and work independently not well elucidated.⁶ Research conducted to date has suggested that most individuals with ASD will require some sort of intervention, often at very intensive levels, throughout adolescence and adulthood, and the estimated costs of medical and non-medical care (e.g., special education, daycare) are prodigiously 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 at \$3.2 million and at about \$35 billion for an entire birth cohort of individuals with autism.⁷ A study of health care utilization in a large group health plan revealed increased medication costs in older children with an ASD when compared with younger children, as well as similarly aged adolescents without an ASD; other care costs were also higher in this population, including a significantly increased rate of hospitalizations.⁸

Costs of transitional and employment programs are also high for young adults with ASD. A recent analysis of U.S. Federal- and State-funded vocational rehabilitation programs showed that enrolled individuals with ASD were among the most costly of nine disability groups examined, with costs even higher among those with ASD and another comorbid disability. These data also showed, however, that those with ASD had a higher rate of employment (40.8 percent) at the time of case closure when compared with those with other disabilities, though with fewer work hours and lower wages than some other disability groups.⁹ One study reported an average expenditure for purchased vocational rehabilitation services of \$3,342 ± \$5,662 in 2005.¹⁰

There is also evidence to suggest that improvements in symptoms and improvements in problem behaviors may slow down or stop after youth with ASD leave high school.¹¹ Many individuals lose access to school- and age-linked services, and many of the services available to adults require waiting lists.^{11, 12} This issue of the lack of services available to help young adults with ASD transition to greater independence has been noted by researchers for a number of years, and is increasingly a topic in the lay media.¹³

The goal of this review is to examine the effects of available interventions among adolescents and young adults with ASD, focusing on the following outcomes: core symptoms of ASD; medical and mental health comorbidities; functional behaviors and independence; the transition to adulthood, and family outcomes.

Interventions Used to Treat ASD

The expression and severity of symptoms of ASD differs widely across individuals and over time. Treatments may include a range of behavioral, psychosocial, educational, medical, and complementary approaches as well as those focused on transitional process and improving outcomes for parents/families of individuals with ASD.

The following sections briefly describe interventions discussed in the literature meeting our criteria for this review. Additional interventions for adolescents and young adults with ASD that did not meet criteria for our review are described in recent systematic and narrative reviews.¹⁴⁻²⁰

Behavioral Interventions

Studies of behavioral interventions available for this review are presented in the broad subcategories of social skills interventions and intensive behavioral interventions.

Social skills interventions. Difficulty with reciprocal social interaction is considered one of the core impairments of ASD. The social impairment seen in ASD takes many forms and can vary greatly from one individual to the next. For adolescents and young adults, social skills interventions often focus on enhancing individuals' interactions with peers and other adults by teaching skills necessary for fluid interaction including instruction perspective-taking, social problem-solving, and understanding social and emotional rules. Skill-based approaches have tried to address social vulnerability through direct group instruction as well as interactive computer based instruction.

Intensive behavioral interventions. Comprehensive intensive behavioral interventions that focus simultaneously on multiple target areas are quite common for preschool children with ASD (e.g., University of California, Los Angeles/Lovaas model and early intensive behavioral intervention variants, Early Start Denver model, parent training paradigms). Studies that use behavioral approaches in an intensive and comprehensive fashion are uncommon during

adolescence and young adulthood, although some programs for older individuals with ASD (not included in this review) may use elements of comprehensive approaches.

Educational Interventions

Most children and adolescents with ASD receive a substantial amount of their treatment in an educational or center-based setting, often beginning early in life (e.g., preschool age). Educational interventions often aim at enhancing specific areas of academic functioning (e.g., reading skills), but also quite frequently attempt to address social, cognitive, and behavioral challenges within an educational setting. In addition to these targets, psychoeducational interventions are also often provided in an attempt to prevent or ameliorate specific areas of behavioral concern (i.e., sleep issues, puberty/sexuality related concerns) and provide family support.

Vocational Interventions

Given the core and associated impairments related to ASD, many young adults exhibit challenges finding and sustaining involvement in appropriate and meaningful vocational activities. A number of interventions related to vocational attainment have focused on developing supportive mechanisms to secure employment. Such approaches often involve an interventionist, such as a job coach, and explicit instruction in the skills necessary to accomplish specific occupational functions. In addition, some approaches have attempted to incorporate instruction in the social and other skills necessary to identify and realize potential employment opportunities (e.g., interviewing).

Adaptive/Life Skills Interventions

While comprehensive behavioral intervention for adolescents and young adults are uncommon, many interventions use applied behavior analysis-based intervention to target and improve important areas of daily functional impairment. These skills, often called adaptive or life skills, vary by specific targets (e.g., feeding, dressing) or more complex tasks (e.g., teaching a sequence of behavior). These interventions may also target reducing challenging behaviors (e.g., self-injury, self-stimulatory behavior, aggression) that interfere with day to day skills and functioning.

Medical and Related Interventions

Medical interventions for symptoms of ASD include pharmacological agents, therapeutic diets, hormonal supplements, hyperbaric oxygen, chelating agents, and many other therapies. Risperidone (age 5 to 16 years) and aripiprazole (age 6 to 17 years), both atypical antipsychotic medications, are the only medical interventions that have U.S. Food and Drug Administration approval for patients with autistic disorder. Other core and related symptoms are treated with medications that are used in an “off-label” fashion. Antipsychotic medications act on the dopamine system and other neurotransmitter systems, such as serotonin.²¹⁻²⁴ Antipsychotic medications are generally divided into typical antipsychotics, which are older and primarily have affinity for dopamine D₂ receptors, and atypical antipsychotics which are newer and show a more diverse receptor profile. Typical antipsychotics studied in ASD include medications like

haloperidol. Atypical antipsychotic medications include risperidone and aripiprazole, which are approved to treat irritability in children with autism, and have moderate and strong evidence of efficacy based upon an earlier systematic review in children with autism spectrum disorder.²⁵

Serotonin reuptake inhibitors (SRIs) are effective in treating anxiety, depression, and obsessive-compulsive disorder. There is overlap between the repetitive behaviors of ASD and obsessive compulsive disorder.^{26, 27} Additionally, high blood levels of serotonin are a biomarker seen in 25 to 30 percent of children with autism, pointing to the serotonin system as a potential target for treatment.^{28, 29} Randomized controlled trials and open-label trials with serotonin reuptake inhibitors in children with ASD have shown some promise but considerable variability in treating repetitive behaviors, anxiety, and aggression.^{25, 30} SRIs include tricyclic antidepressants and more selective inhibitors. The newer class of SRIs, selective serotonin reuptake inhibitors, include fluvoxamine, sertraline, and fluoxetine.

Opioid antagonists have been used in patients with ASD based upon the hypothesis that the opioid system may be involved in maintaining or reinforcing self-injurious behaviors.³¹ Naltrexone is one opiate antagonist that has been investigated for treatment of self-injury, hyperactivity, or stereotyped movements in children with autism; although without evidence from randomized controlled trials favoring its use.³²⁻³⁴

Allied Health Interventions

Several allied health interventions address core symptoms of ASD as well as associated difficulties and deficits. Social communication vulnerabilities are considered core features of ASD. As such, language difficulties and nonverbal communication challenges are often important targets of treatment. Historically, one communication intervention, facilitated communication, focused on helping individuals with communication and language challenges communicate via an interventionist or facilitator. More recently, interventions have utilized technology and augmentative communication therapies/devices in improving communication skills in individuals with ASD.

Other approaches have focused on teaching specific aspects of speech and language development (i.e., production, pragmatic language interventions). A number of additional interventions include occupational therapy techniques, movement and music therapies, as well as approaches aimed at sensory integration or addressing challenging sensory behaviors.

Importance of This Review

Current data suggest that attainment of independent living or employment in adulthood for individuals with an ASD is variable, with factors that predict the ability to live and work independently not well elucidated.⁶ Available data suggest that individuals with ASD will require some sort of intervention throughout adolescence and adulthood, and the estimated costs of medical and non-medical (e.g., special education, daycare) care are prodigiously high.²⁰ One study estimates that the total yearly societal per capita cost of caring for and treating a person with autism in the United States at \$3.2 million and at about \$35 billion for an entire birth cohort of individuals with autism.⁷ A study of healthcare utilization in a large group health plan revealed increased medication costs in older children with ASD as compared with younger children as well as similarly-aged adolescents without ASD; other care costs were also higher in this population, including a significantly increased rate of hospitalizations.⁸

Costs of transitional and employment programs are also high for young adults with ASD. A recent analysis of U.S. federal and state-funded vocational rehabilitation programs showed that the prevalence of ASD among those in training programs increased from 0.2 percent to 0.6 percent from 2002 to 2006; those with ASD were among the most costly of nine disability groups examined, with costs even higher among those with ASD and another comorbid disability. These data also showed, however, that those with ASD had a higher rate of employment (40.8 percent) at the time of case closure as compared with those with other disabilities, though with fewer work hours and lower wages than some other disability groups.⁹

There is no cure for ASD and currently no global consensus regarding 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 autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. Investigators in the area have noted that less research on therapies for adolescents or young adults exists than for younger children,³⁵ and such research is increasingly critical as the prevalence of ASD continues to grow and as children with ASD diagnoses reach adolescence.

Scope and Key Questions

Scope of the Report

We focused this review on interventions for adolescents and young adults between the ages of 13 and 30 with ASD (Autistic Disorder, Asperger syndrome, Pervasive Developmental Disorder-Not Otherwise Specified) and addressed questions related to the effectiveness of therapies targeting core symptoms of ASD (impairments in communication, social interaction, and behavior); aimed at common medical or mental health comorbidities, which include associated symptoms such as irritability; addressing the process of transitioning to adulthood; and addressing family outcomes.

Key Questions

We have synthesized evidence in the published literature to address these key questions:

Key Question 1: Among adolescents and young adults with autism spectrum disorders (ASD), what are the effects of available interventions on the core symptoms of ASD?

Key Question 2: Among adolescents and young adults with ASD, what are the effects of available interventions on common medical and mental health comorbidities (e.g., epilepsy, sleep disorders, motor impairments, obesity, depression, anxiety, acute and episodic aggression, ADHD, etc.)?

Key Question 3: Among adolescents and young adults with ASD, what are the effects of available interventions on functional behavior, attainment of goals toward independence, educational attainment, occupational/vocational attainment, life satisfaction, access to health and other services, legal outcomes, and social outcomes?

Key Question 4: Among adolescents and young adults with ASD, what is the effectiveness of interventions designed to support the transitioning process, specifically to affect attainment of goals toward independence, educational attainment, occupational/vocational attainment, life satisfaction, access to health and other services, legal outcomes, and social outcomes?

Key Question 5: Among adolescents and young adults with ASD, what harms are associated with available interventions

Harms are defined by the Evidence-based Practice Center Program as all possible adverse consequences of an intervention, including adverse events.

Key Question 6: What are the effects of interventions on family outcomes?

Organization of This Evidence Report

The Methods section describes our processes including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and our method for extraction of data into evidence tables and compiling evidence. We also describe our approach to grading of the quality of the literature and to evaluating the strength of the body of evidence.

The Results section presents the findings of the evidence report, synthesizing them by category of intervention, key question, and outcomes reported. We report the number and type of studies identified and we differentiate between total numbers of publications and unique studies. The final section of the report discusses key findings and expands on methodologic considerations relevant to each key question. We also outline the current state of the literature and challenges for future research in ASD in the target age range.

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
- Appendix B. Categorization of Study Designs
- Appendix C. Data Extraction Forms
- Appendix D. Evidence Tables
- Appendix E. Quality Assessment Form
- Appendix F. List of Excluded Studies
- Appendix G. Quality of the Literature

We also include a list of abbreviations and acronyms at the end of the report.

Uses of This Report

This evidence report addresses the key questions outlined previously using methods described in the report to conduct a systematic review of published literature. We anticipate that the report will be of value to clinicians who treat individuals with ASD, including pediatricians, psychologists, psychiatrists, allied health professionals, and other clinicians who provide care for ASD.

In addition, this review will be of use to the National Institutes of Health, Centers for Medicare & Medicaid Services, and the Health Resources and Services Administration—all of which have offices or bureaus devoted to developmental issues. This report can bring practitioners up to date about the current state of evidence, and it provides an assessment of the quality of studies that aim to determine the outcomes of therapeutic options for the management of ASD. It will be of interest to individuals affected by ASD and their families because of the high prevalence of ASD, significant personal costs associated with it, and the recurring need for individuals with ASD, their families, and their health care providers to make the best possible decisions among numerous options.

Researchers can obtain a concise analysis of the current state of knowledge in this field. They will be poised to pursue further investigations that are needed to understand best approaches to therapies for adolescents and young adults with ASD.

Methods

Topic Development and Refinement

The topic for this report was nominated 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 adolescents and young adults with autism spectrum disorders (ASD). After review from the Agency for Healthcare Research and Quality (AHRQ), the questions and framework were posted to a public Web site. The public was invited to comment on these questions.

After reviewing the public commentary, we drafted final key questions and submitted them to AHRQ for review. We identified technical experts on the topic of ASD in adolescents and young adults to provide assistance during the project. TEP members represented the clinical and research communities from a range of perspectives. They were invited to participate based on our commitment to engaging a range of experts who could help solidify the decisional dilemmas facing individuals and families with ASD. They included both researchers and clinicians with expertise in behavioral, medical, social, psychological and educational issues. The Technical Expert Panel (TEP) contributed to AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included 6 members serving as technical or clinical experts. 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 at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on assessing the quality of the literature.

Role of the AHRQ Task Order Officer

The Task Order Officer (TOO) was responsible for overseeing all aspects of this project. The TOO help 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.

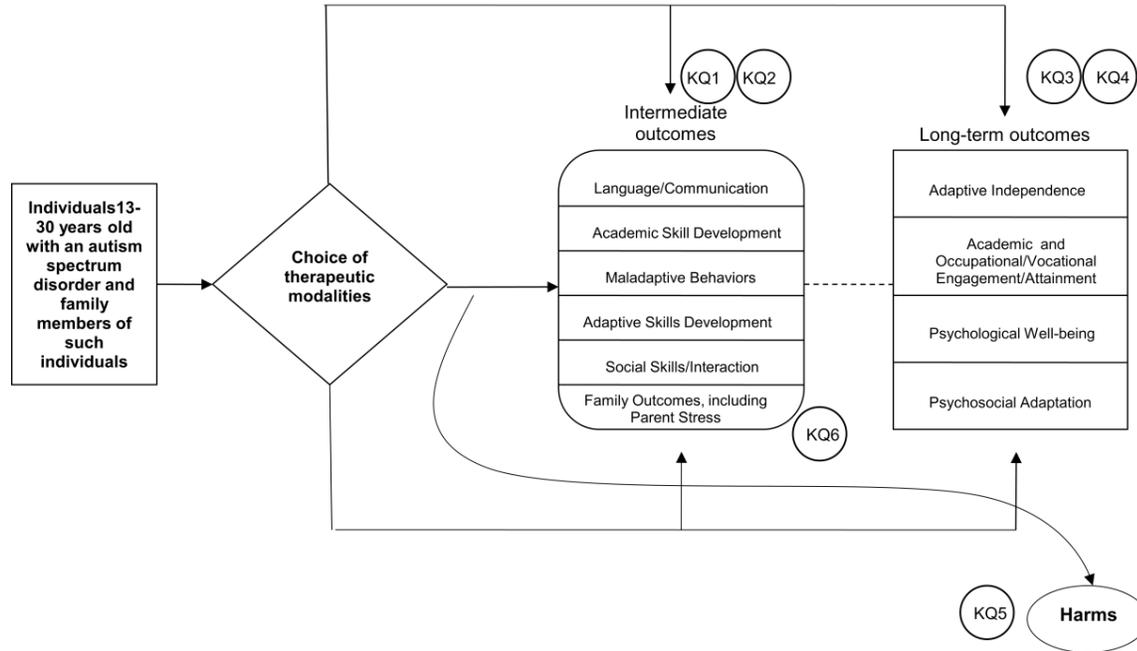
Analytic Framework

We developed the analytic framework (Figure 1) based on clinical expertise and refined it with input from our key informants, focus group of family members, and TEP members. The framework summarizes the process by which individuals with ASD and their families/caregivers make and modify treatment choices. Treatment choices include surgical or nonsurgical approaches and may lead to intermediate outcomes including changes in communication skills, academic skill development, or social skills. Interventions may also lead to long-term outcomes such as adaptive independence and changes in psychosocial well-being. Interventions may also lead to changes in family outcomes such as parent distress and may be associated with

harms/adverse effects. Numbers in circles within the diagram indicate the placement of key questions in relation to the treatment process.

Figure 1. Analytic Framework for Interventions for Adolescents and Young Adults with ASD

Interventions for Adolescents and Young Adults With Autism Spectrum Disorders



ASD=autism spectrum disorders; KQ=key question.

Literature Search Strategy

Databases

An expert librarian employed search strategies provided in Appendix A to retrieve research on therapies for adolescents and young adults with ASD. Our primary literature search employed 4 databases: MEDLINE® via the PubMed interface, PsycINFO (psychology and psychiatry literature), the Educational Resources Information Clearinghouse, and the Cumulative Index of Nursing and Allied Health Literature database. 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 1980 and the publication of standardized diagnostic criteria for ASD (i.e., *Diagnostic and Statistical Manual of Mental Disorders III*)

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.

Regulatory Information

The AHRQ Scientific Resource Center also searched for information on the following specific medications and interventions used to treat ASD. We requested grey literature information on these drugs and devices as they are either approved by the U.S. Food and Drug Administration to treat irritability in ASD or are beginning to be used in the ASD population and have not yet been well-reported in the published literature (i.e., hyperbaric oxygen):

- Risperidone
- Aripiprazole
- Hyperbaric oxygen chambers.

The Scientific Resource Center sought grey literature in resources including the websites of the Food and Drug Administration and Health Canada and clinical trials registries such as ClinicalTrials.gov. We also gave manufacturers of these medications and devices an opportunity to provide additional information, though none did so.

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 and from 1980 to the present. Our searches were executed between September 2010 and May 2011. 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 and exclusion criteria

Category	Criteria
Study population	Adolescents or young adults (ages 13-30) with ASD (autistic disorder, Asperger syndrome, PDD-NOS) or families/caregivers of individuals with ASD between the ages of 13-30
Interventions	Interventions aimed at ameliorating core symptoms of ASD, affecting independent functioning, adaptive behavior, or the transition process, or targeting family outcomes
Comparators	Placebo Other intervention
Outcomes	Social skills/interaction, language and communication, repetitive and other maladaptive behaviors, motor outcomes, psychological distress, adaptive skills development, academic skills development, and family outcomes including family distress and family satisfaction
Time period	Studies published from 1980–present with no limits on timing of outcomes
Setting	Any setting including educational, residential, and clinic

Table 1. Inclusion and exclusion criteria (continued)

Category	Criteria
Publication languages	English only
Admissible evidence (study design and other criteria)	<p><u>Admissible designs</u></p> <ul style="list-style-type: none"> Controlled trials, observational studies including prospective and retrospective cohort studies, prospective and retrospective case series <p><u>Study size</u></p> <ul style="list-style-type: none"> N ≥ 20 individuals between 13-30 years of age with ASD or family members of such individuals <p><u>Other criteria</u></p> <ul style="list-style-type: none"> Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results Patient populations must include adolescents or young adults (13-30 years of age) with ASD or families/caregivers of individuals with ASD between the ages of 13-30 Studies must address one or more of the following: <ul style="list-style-type: none"> Treatment modality aimed at modifying ASD core symptoms, common comorbidities, family-related outcomes, or assisting with transitional issues Outcomes (including harms) related to interventions for ASD Studies must include extractable data on relevant outcomes, including data presented in text or tables (vs. solely in figures) Studies must present aggregate data (vs. only data for each individual participant)

ASD=autism spectrum disorders; N=number; PDD-NOS=Pervasive Developmental Disorder-Not Otherwise Specified.

Study Population

Studies needed to provide adequate information to ensure that participants fell within the target age range of age 13 to 30. We selected the lower bound of 13 as a previous AHRQ comparative effectiveness review of therapies for children with ASD included studies with individuals ≤ age 12.³⁶ We used the upper bound of 30 as individuals with ASD can remain in the secondary school system until age 21 and may not experience the transition to more independent functioning in their twenties as would be expected for typically developing individuals. The upper age of 30 accounted for potential developmental delays in individuals with ASD.

For studies with populations including individuals with ASD either under the age of 13 or over age 30, we retained the study if we could infer that at least 50 percent of the study participants were in the 13 to 30 age range or if the mean age of participants was in the 13 to 30 age range. 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.

We note that if a research study used a comparison group that did not contribute to an estimate of the contrast of interest in our review, we included the one arm of the study that was relevant. For example, an intervention study in which the intervention group is individuals with ASD and the comparison group is a group of individuals with Down Syndrome would not provide an estimate of the effect of the intervention for children with ASD. Rather than exclude this study, we include the group of individuals with ASD as a case series.

Sample Size

We excluded studies that included fewer than 20 total participants in the target age range with ASD or family members of such individuals. Our goal was to identify and review the best evidence for assessing the efficacy and effectiveness of therapies for adolescents and young adults with ASD, with an eye toward utility in the treatment setting. Interventions to address ASDs 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 20 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 20 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 study designs except individual case reports, and our approach to categorizing study designs is presented in Appendix B.

Outcomes

We assessed outcomes in the broad areas of social skills/interaction, language and communication, repetitive and other maladaptive behaviors, motor outcomes, psychological distress, adaptive skills development, academic skills development, and family outcomes including family distress and family satisfaction related to interventions. 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 considered changes in long-term functional outcome areas, including adaptive independence/self care, academic/occupational/vocational engagement and attainment, psychological well-being, psychosocial adaptation, residential outcomes, legal outcomes, social/relationship-focused outcomes (interpersonal relationships, community involvement/societal participation, self-actualization and acceptance, etc.), access to health services (conservatorship, access to day care, access to health care, access to social, financial, and other support systems), and use of public programs.

We also assessed the harms of interventions, defined by the Evidence based Practice Center program as the totality of adverse consequences of an intervention.³⁷ Harms may include:

- Adverse behavioral or psychosocial reactions to behavioral or other therapies (e.g., increased aggression or anxiety)
- Regression of language, skills, or behaviors
- Increases in or worsening of comorbid symptoms
- Adverse reactions to drug therapies (e.g., somnolence, weight gain)
- Reduction in and negative influences on quality of life

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 C). 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 C) 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.

Categorization of Interventions

Interventions to treat ASD overlap substantially¹⁴ and cleanly identifying the category into which an intervention should be placed is difficult. We adapted the categorization approach we used in our previous review of therapies for children with ASD,³⁶ and studies fell into the following categories:

- **Behavioral interventions.** We defined behavioral interventions to include intensive behavioral and developmental interventions and social skills interventions employing either peer group- or computer-based approaches.
- **Educational interventions.** Educational interventions are those focusing on improving educational and cognitive skills and intended primarily to be administered in educational settings, or studies for which the educational arm was most clearly categorized.
- **Adaptive/life skills-focused interventions.** We considered those interventions focused on developing skills to assist with independent functioning and independent execution of activities of daily living as falling within this category. Interventions described in this review include interventions targeting transitioning to a new school routine, self-care, and cognitive aids.
- **Vocational interventions.** We classified interventions targeting job skills, employment supports, or placing individuals into work as vocational interventions. Such interventions included in the literature meeting our criteria for this review comprise sheltered workshops, supported employment, and vocational rehabilitation.
- **Medical and related interventions.** We broadly defined medical and related interventions as those that included the administration of external substances to the body in order to treat symptoms of ASD; medical interventions represented in the literature included in this review comprised prescription medications.
- **Allied health interventions.** Allied health interventions included therapies typically provided by occupational and physical therapists, including facilitated communication, music therapy, and recreational therapies.

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 designed the tables to provide sufficient information to enable readers to understand the studies, including issues of study design, descriptions of the study populations (for applicability), description of the intervention, and baseline and outcome data on constructs of interest.

The team abstracted several articles into the evidence table and then reconvened as a group to discuss the utility of the table design. We repeated this process through several iterations until we decided that the table included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence 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, what constituted assessment of treatment fidelity). related to the data extraction process. In addition to outcomes related to treatment effectiveness and family outcomes, 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 D. 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.

Individual Study Quality Assessment

We used a components approach to assessing the quality of individual studies, following methods outlined in the Evidence based Practice Center's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.³⁸ Decision rules regarding application of the tools were developed *a priori* by the research team. In some instances, it was appropriate to apply specific questions only to one body of literature (e.g., treatment fidelity to behavioral studies and medication adherence to medical studies) and we note those cases where appropriate. We assessed each domain individually and combined them for an overall quality level as described below. Three levels were possible: good, fair, and poor (Table 2). Appendix E includes the questions we used to assess each domain.

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 on all questions to receive a rating of good quality. We required that studies receive positive ratings on the following questions for a fair rating:

- Did the study employ a group design?
- Was there an appropriate comparison group?
- Was a systematic diagnostic approach used within the study?
- Were inclusion and exclusion criteria clearly stated?
- Was the intervention fully described?
- Did outcome measures demonstrate adequate reliability and validity?
- Were outcome data collected from sources appropriate to the target outcome?
- Was an appropriate statistical analysis used?

We rated studies without positive scores on these questions as poor quality and retained poor quality studies as part of the evidence base.

Data Synthesis

There was significant heterogeneity among studies reporting therapeutic results of interventions for adolescents and young adults with ASD, including heterogeneity of population characteristics, heterogeneity of interventions, and heterogeneity of outcome measures. Therefore, it was not appropriate to perform any meta-analysis.

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 Evidence based Practice Center's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*³⁹ and are based on consideration of four domains: risk of bias, consistency in direction of the effect, directness in measuring intended outcomes, and precision of effect (Table 3). Strength of evidence is assessed separately for major intervention-outcome pairs.

Table 3. Domains used to assess strength of evidence^a

Domain	Explanation
Risk of bias	Degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: <ul style="list-style-type: none"> • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies
Consistency	Degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: <ul style="list-style-type: none"> • Effect sizes have the same sign (that is, are on the same side of “no effect”) • The range of effect sizes is narrow
Directness	Relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Evidence is indirect if: <ul style="list-style-type: none"> • It uses intermediate or surrogate outcomes instead of ultimate health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes • It uses two or more bodies of evidence to compare interventions A and B, e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest.
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately). If a meta-analysis was performed, this will be the confidence interval around the summary effect size.

^a Excerpted from Owens et al., 2010³⁹

Based on the approach used in the prior AHRQ review of therapies for children with ASD,³⁶ we required at least three fair quality studies to be available to assign a low strength of evidence rather than considering it to be insufficient. For determining the strength of evidence for effectiveness outcomes, we only assessed the body of literature deriving from studies that included comparison groups. 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. For determining the strength of evidence related to harms, we also considered data from case series.

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.

Applicability

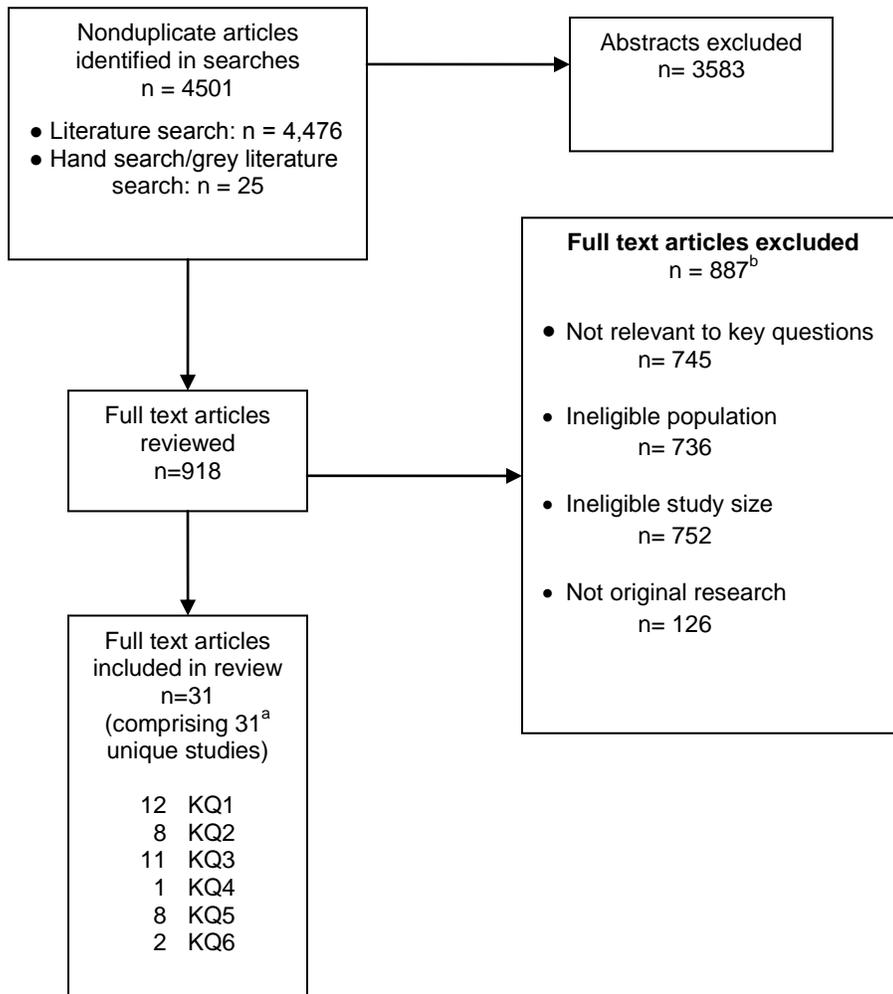
Finally, it is important to consider the ability of the outcomes observed to apply both to other populations and to other settings (especially for those therapies that take place within a clinical/treatment setting but are hoped to change behavior overall). Our assessment of applicability included determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category.

Results

Article Selection

We identified few studies addressing interventions for adolescents and young adults with autism spectrum disorders (ASD). Of the entire group of 4501 citations identified, 918 required full text review (Figure 2). Of these 918 full text articles reviewed, we retained 31 papers (comprising 31 unique studies) and excluded 887 papers. Reasons for article exclusion are listed in Appendix F.

Figure 2. Disposition of studies identified for this review



^aOne paper⁴⁰ reports two unique studies

^b Numbers do not tally as studies could be excluded for multiple reasons
KQ=key question; n=number.

Organization of Results

As noted, we classified studies by broad category of intervention (behavioral, educational, vocational, adaptive/life skills, medical, and allied health). With the exceptions of studies of medical and vocational interventions, which included at least two studies addressing the same intervention, the other categories of interventions largely comprise single studies of unique interventions. Most studies (n=12) also targeted core symptoms of ASD (Key Question 1) or functional behavior/independent living skills (n=11) (Key Question 3). Eight studies, all of medical interventions, examined comorbidities commonly occurring with ASD, which we defined broadly to encompass associated symptoms such as irritability, and harms of interventions (Key Question 2, 5).

One study addressed interventions targeting the transition process (Key Question 4), and two assessed effects of an intervention on family outcomes (Key Question 6). Because questions were addressed by a number of small, single studies of a given intervention, we discuss all studies together in the following sections instead of divided by key question. This approach allows us to present the findings of this disparate literature more clearly. We use headings to indicate the outcomes (e.g., core symptoms, functional behavior, harms, etc.) targeted in each study.

We present findings beginning with an overview of the content of the literature as a whole, including the range of study designs used, approaches assessed and participants included. The detailed analysis of the literature provides further discussion and analysis of studies presented by broad category of intervention. Studies also are described in more detailed summary tables in the relevant section of text. For information on studies not included in the summary tables, please see the evidence tables in Appendix D; for information on quality scores for each study, see Appendix G.

Overview of the Literature

The 31 unique studies described in this review included ten randomized controlled trials (RCTs). Table 4 provides an overview of the characteristics of the literature overall.

Table 4. Overview of the literature addressing interventions for adolescents and young adults with ASD

Characteristic	RCTs	Nonrandomized trials	Prospective cohort studies	Prospective case series	Retrospective case series	Total Literature
Total n:	10	3	4	9	5	31
Intervention category						
Behavioral	2	1	1	2	0	6
Educational	1	1	0	0	0	2
Adaptive/Life Skills	1	0	1	2	1	5
Vocational	0	2	1	0	2	5
Medical	5	0	0	2	1	8
Allied Health	1	0	0	3	1	5
Treatment Duration						
<1 month	3	0	0	2	0	5
>1 to ≤3 months	5	1	1	5	0	12
>3 to ≤6 months	0	1	0	0	1	2
>6 to ≤12 months	2	0	1	1	0	4
>12 months	0	1	2	1	2	6
Not specified	0	0	0	0	2	2
Study population						
United States	5	1	1	6	4	17
Europe	3	2	3	1	1	10
Asia	2	0	0	2	0	4
Total N participants with ASD	341	114	172	304	1,940^a	2,871

^aThis figure includes 1,707 individuals with ASD included in one study reporting data from an administrative database.¹⁰ ASD=autism spectrum disorders; n=number; RCT=randomized controlled trial

We did not rate any study as good quality. Five studies were fair quality,⁴¹⁻⁴⁵ and most studies were poor quality.^{10, 12, 40, 46-68} Seventeen studies included comparison groups, and ten of these studies were randomized. Most studies were conducted in the United States or Europe, and participant ages across all studies ranged from 2 years to over 45 years. Only studies of medical interventions reported harms data.

Studies of Behavioral Interventions

Key Points

- Six behavioral studies examined social skills and intensive behavioral interventions and included individuals with ASD both with and without concomitant intellectual disability or language deficiencies. All studies were of poor quality.
- Most studies reported short-term gains in social skills as reported by parents or within study measures.

- Few studies reported evidence of generalization of skills beyond the treatment context.

Overview of the Literature

We identified six studies^{40, 54-57} of behavioral interventions in six unique populations (Table 5). Studies included two RCTs conducted in the United States⁵⁴ and United Kingdom⁵⁶ and two case series conducted in Canada⁵⁵ and Italy.⁵⁷ One paper presented data from two separate studies conducted in the United Kingdom and involving two unique groups of participants.⁴⁰ Individuals in both studies received the same computer-based social skills software intervention, but comparators differed, and participants were randomized to intervention or control groups in only one study.⁴⁰ Four studies examined either group^{54, 55} or computer-based intervention approaches^{40, 56} focused on social skill development, including recognizing emotions, for individuals with ASD. One study conducted in Italy examined the impact of intensive behavioral treatment from a semi-residential rehabilitation center on adaptive behavior.⁵⁷

Participants ranged in age from 13 to 43 in four studies. One study⁵⁷ did not provide precise age data but notes that 34 participants were categorized as adolescents. Treatment duration ranged from 2 weeks to 2 years. We rated all studies as poor quality. Appendix G provides the quality ratings for each study.

Detailed Analysis

Behavioral Studies Addressing Core Symptoms of ASD

Social skills interventions. Most studies of behavioral interventions addressing effects on the core symptoms of ASD were short term and included a small number of individuals (Table 5). Among studies examining group-based social skills programs, one RCT examined the short-term outcome of a trial of a manualized (i.e., has a published treatment manual) outpatient social skills program, the Program for the Education and Enrichment of Relational Skills (PEERS).⁵⁴ The study included 33 adolescents (mean age 14.6 years) randomized either to a 12-week program of group social skills intervention or to a delayed treatment control group. At completion of the group-based treatment, individuals in the intervention group, who possessed average cognitive abilities (Mean intelligence quotient [IQ]=96.0), demonstrated improvements in social skills knowledge and parent-rated social skills and reportedly were participating in more frequent social activity. No differences were found in teacher-reported social functioning.

A prospective case series also examined the impact of a 12-week social skills group for adolescents (mean age 14.6 years) with ASD. Adolescents recruited from community clinics with verbal skills sufficient to participate in a group intervention demonstrated parent-reported improvements related to problem behaviors and autism specific social concerns.⁵⁵

Computer-based interventions. Among studies examining computer-based approaches, one RCT of a computer-based social skills training for adolescents with ASD randomized 22 children (age 12 to 18) to either training through 10 half-hour sessions with a computer program designed to train emotion recognition or to a control group.⁵⁶ The intervention group demonstrated fewer errors within the program from pre to post training, and relative to controls demonstrated improvement regarding emotion recognition on via tasks presented within cartoons and stories.

In an additional study examining emotion recognition abilities in relation to a computer based training program,⁴⁰ across both experiments utilizing self-guided and group-supported

approaches adults with ASD completing the program demonstrated improvements in recognizing faces and voices utilized in the training relative to the control group but did not demonstrate such improvements in recognizing improvements outside of the tasks.

Intensive behavioral interventions. The one study examining an intensive behavioral approach reported on the impact of intensive behavioral treatment from a semi-residential rehabilitation center on adaptive behavior.⁵⁷ The study included 34 adolescents (age range not provided) receiving intervention from autism specific centers in Italy. Participants were reported to have improved on measures of socialization and adaptive behavior.

Table 5. Key outcomes of behavioral studies addressing the core symptoms of ASD

Author, year, country Groups, N enrollment / N final Study quality	Age, mean/yr ± SD IQ, mean ± SD	Key outcomes
Group-based Social Skills Training		
Laugeson et al., ⁵⁴ 2009 United States G1: Immediate social skills training, 35 (total)/17 G2: Wait list, 35 (total)/16 Quality: Poor	G1: 14.6 ± 1.3 G2: 14.6 ± 1.6 IQ (KBIT2): G1: 96 ± 16.1 G2: 88.3 ± 21.1	<ul style="list-style-type: none"> • 12-week manualized intervention: Program for the Education and Enrichment of Relational Skills • School-aged children of average intelligence demonstrated short-term improvements in social skills knowledge, parent rated skills, and reported engagement in social activity. • Teacher rated outcomes were not different for delayed treatment control.
Tse et al., ⁵⁵ 2007 Canada G1: Social skills training with emphasis on learning through role play, 46/32 Quality: Poor	G1: 14.6 ± 1.7 NR	<ul style="list-style-type: none"> • 12-week intervention for adolescents with substantial verbal ability. • Improvement in parent rated skill outcomes. • Non-manualized intervention, no comparison group, and only parent report outcomes noted.
Computer-based Social Skills Training		
Golan et al., ⁴⁰ 2006 United Kingdom Study1 G1: Home software users, 19/NR (21% drop out rate) G2: Control, 22/NR Quality: Poor	G1: 30.5 ± 10.3 G2: 30.9 ± 11.2 IQ (WASI, verbal): G1: 108.3 ± 13.3 G2: 109.7 ± 10.0	<ul style="list-style-type: none"> • Individuals participating in home-based program demonstrated improvement related to emotion recognition of faces and voices within the study relative to controls. • Individuals did not perform differently on measures assessing generalization of emotion recognition.
Golan et al., ⁴⁰ 2006 United Kingdom Study 2 G1: Software and tutor, 18/13 G2: Social skills course, 18/13 Quality: Poor	G1: 25.5 ± 9.3 G2: 24.4 ± 6.4 IQ (WASI, verbal): G1: 105.7 ± 16.1 G2: 96.5 ± 15.5	<ul style="list-style-type: none"> • Individuals participating in home-based program plus group intervention demonstrated improvement related to emotion recognition of faces and voices within the study relative to controls. • Individuals did not perform differently on measures assessing generalization of emotion recognition. • Verbal IQ was significantly associated with improvement.

Table 5. Key outcomes of behavioral studies addressing the core symptoms of ASD (continued)

Author, year, country Groups, N enrollment / N final Study quality	Age, mean/ yrs ± SD IQ, mean ± SD	Key outcomes
Computer-based Social Skills Training		
Silver et al., ⁵⁶ 2001 United Kingdom G1: Computer sessions + standard lessons, 12/10 G2: Standard lessons only, 12/11 Quality: Poor	G1: 13.9 ± 0.9 G2: 14.75 ± 2.0 IQ (BPVS): G1: 10.67 ± 2.25 G2: 12.0 ± 3.33	<ul style="list-style-type: none"> School aged children and adolescents with substantial verbal abilities demonstrated improvement in emotion recognition after ten half hour sessions over 2-weeks. No measures of generalization or outcomes apart from the study session were included.
Intensive behavioral treatment		
Valenti et al., ⁵⁷ 2010 Italy G1: ABA-based intensive behavioral therapy, 34/34 Quality: Poor	G1: NR, 34 identified as post-pubertal adolescents 25/34 identified as having intellectual disability	<ul style="list-style-type: none"> Study of treatment received within context of semi-residential facility indexed gains related to adaptive behavior. No control group was included, the participants were very diverse, and the specific intervention components were not well described. Parent satisfaction with the treatment program was high on all measures.

BPVS=British Picture Vocabulary Scale; IQ=intelligence quotient; KBIT2=Kaufman Brief Intelligence Test-Second Edition; n=number; NR=not reported; SD=standard deviation; WASI=Wechsler Abbreviated Scale of Intelligence

Behavioral Studies Addressing Independent Functioning

Intensive behavioral interventions. In the poor quality case series assessing the impact of intensive behavioral treatment,⁵⁷ participants demonstrated modest improvements in standard measures of adaptive behavior over a 2 year period. Female participants also improved in daily living and motor skills in this uncontrolled study.

Behavioral Studies Addressing Family Outcomes

Intensive behavioral interventions. The same poor quality case series⁵⁷ investigated family satisfaction with an intensive behavioral approach. The study included both adolescents and younger children and presented satisfaction data for the two groups combined. Overall, parents were highly satisfied with most elements of the program at year 1 and year 2, with median scores in the 4.5 to 10 range on scales ranging from 1 to 6 or 1 to 10. The overall median score for the domain of “family participation” increased slightly (8.0 to 8.5) as did scores on individual domain elements (“feeling of a having a say in the matter,” 5.0 to 5.5; “involvement in school meetings,” 5.0 to 5.5). Scores in the domain of “intervention outcome” remained stable for elements including “service to help participant in facing daily problems” (5.0), “feeling confident about what to do” (5.0), and “service to help participants’ quality of life” (5.0) but declined slightly on “service to help family in coping with problems” (5.0 to 4.5).

Studies of Educational Interventions

Key Points

- Two poor quality studies evaluated educational approaches.
- Strategies to increase reading comprehension were associated with some improvement in a small, poor quality study.
- Neither vocabulary teaching method assessed in one study was significantly more effective in increasing nouns learned by individuals with ASD and intellectual disability.

Overview of the Literature

Two studies, both poor quality, examined educational interventions. One nonrandomized controlled trial⁵⁹ conducted in the United States included 23 individuals ranging in age from 17 to 37 years (mean=26) with mean mental age scores of 3.3 years and mean language scores of 3.0 years. Participants received language instruction using 2 methods of teaching over the course of 8 weeks, and investigators assessed outcomes including the number of nouns learned and retained. One RCT⁵⁸ was conducted in Canada and investigated procedural strategies to promote reading comprehension and included 20 individuals with ASD (mean age=15.1, mean Stanford-Binet IQ=88.15 ± 16.06). Appendix G provides the quality ratings for each study.

Detailed Analysis

Educational Studies Addressing Core Symptoms of ASD

One poor quality nonrandomized trial included 23 adults with ASD and intellectual disability living in a residential treatment facility (Table 6).⁵⁹ Participants ranged in age from 17 to 37 (mean=26) and had mean mental age scores of 3.3 years and mean language scores of 3.0 years. Investigators matched participants on chronological age, mental age and vocabulary scores, and duration of stays in residential treatment and assigned groups to either analog language teaching for three 15 minute individual sessions/week over 4 weeks or natural language teaching for three 45 minute group sessions/week over 4 weeks. After an assessment, participants crossed over to the alternate training condition.

At the end of this second training phase, investigators assessed vocabulary retention. Neither teaching condition was significantly better at increasing vocabulary (mean number nouns learned in analog condition=15.7, mean learned in natural language condition=12.8); as expected, generalization was greater during receptive as compared with expressive testing of noun identification ($p<0.001$).⁵⁹ Participants retained an average of 92.2 percent of items learned at the final assessment. Participants' level of intelligence was related to the amount of generalization and to order of teaching. Participants in the upper range for mental age scores learned more nouns with analog teaching first (mean nouns learned=64.8) than did those in the middle range (mean nouns learned=10.3). Participants in the lowest mental age range performed more poorly than others regardless of teaching condition order.

Table 6. Key outcomes of educational interventions addressing core symptoms of ASD

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
Elliott et al., ⁵⁹ 1991 United States G1: 23/23	G1: 26 G1: NR	<ul style="list-style-type: none"> Analog and natural language teaching styles had similar effects on increasing the number of nouns learned by participants.
Quality: poor		
G=group; NR=not reported		

Educational Studies Addressing Independent Functioning

A poor quality randomized study investigating the use of procedural strategies to promote reading comprehension included 20 individuals with high-functioning ASD (mean age=15.1, mean Stanford-Binet IQ=88.15 ± 16.06).⁵⁸ Investigators presented participants with 5 stories written at a roughly sixth grade reading level in various procedural facilitation conditions or two control conditions. Procedural facilitation conditions included pre-reading, in which investigators asked participants questions designed to elicit common knowledge relevant to the main focus of the story; anaphoric cuing, in which a number of pronouns in each passage were underlined with choices for appropriate or inappropriate referent words appearing below them; and a cloze (fill in the blank) condition, in which blanks in sentences in each story could be completed by referring to information presented in the preceding sentences. Passages were not altered in the control condition. Investigators also asked participants questions about the stories' main idea, facts from the stories, and for their own retelling of the stories to gauge their understanding of the content. Participants read and answered questions about all 5 stories, presented in random order for each participant, in approximately 60 minutes, scored independently by masked assessors on a 1 (low) to 25 (high) point scale. Reading comprehension scores ranged from 12.79 ± 6.33 in a control condition to 15.41 ± 6.28 in the anaphoric cuing condition.

Overall, the study reported a medium size effect for procedural facilitation ($F(4,76)=2.49$, $\eta^2=0.12$, $p=0.05$). Post-hoc analyses also revealed a significant effect of anaphoric cuing on passage comprehension with a medium effect size ($F(1,19)=5.60$, $\eta^2=0.42$, $p=0.03$). No significant effect of prereading questions or cloze (fill in the blank) were apparent in the results. Correlation analyses showed that anaphoric cuing worked best for individuals with lower grammatical ability while prereading questions were most effective for students with high pre-existing comprehension ability (Table 7).⁵⁸

Table 7. Key outcomes of educational interventions addressing independent functioning

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
O'Connor et al., ⁵⁸ 2004 Canada G1: 20/20 Quality: Poor	G1: 15.11 ± 0.99 G1: 88.15 ± 16.06	<ul style="list-style-type: none"> • Medium effect size for procedural facilitation and anaphoric cuing styles as compared with baseline (p=0.05 and p=0.03, respectively) among high functioning individuals with ASD • No significant effect of prereading questions or cloze style prompting.

ASD=autism spectrum disorders; G=group

Studies of Adaptive/Life Skills Interventions

Key Points

- Five poor quality studies reported on disparate adaptive/life skills-focused interventions; three studies assessed outcomes after short-term (<12 weeks) intervention, and most included individuals with intellectual disability and ASD.
- Studies reported some improvements in very specific life skills (e.g., shoe lacing, building exiting, digital device use) after specific short-term interventions.
- A study comparing a Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH)-based residential facility with group homes, institutions, or family homes reported more communication adaptations, socialization programming, preventive behavior management approaches, and visual structure than the other settings.
- In the single study addressing transitional processes, a rotating classroom schedule did not significantly increase crisis events in adolescents with ASD.

Overview of the Literature

We identified five studies, all of poor quality, of adaptive-focused interventions (Table 8).⁴⁶⁻⁵⁰ Appendix G provides the quality ratings for each study. Treatment duration varied from a day-long experiment to roughly 2 years in a residential facility. All studies were conducted in the United States, and at least three included participants with intellectual disability.⁴⁶⁻⁴⁸ One cross-over RCT included 20 participants with ASD with mean ages between 11.5 and 13.1 and mean developmental ages (Psychoeducational Profile) of 3.0 to 3.1.⁴⁸ Outcomes assessed included the number of trials needed to learn to lace a color coded shoe vs. a non-color coded shoe.

One cohort study assessed an implementation of the TEACCH psychoeducational model emphasizing farming and landscaping as vocational modalities and focused on teaching skills and ameliorating behavioral problems.⁴⁶ The mean age of the 32 participants at baseline was 25 (range=16 to 48 years). Eighty-five percent had severe to profound intellectual disability (Vineland Adaptive Behavior Composite mean=25), and most had moderate to severe autism (mean Childhood Autism Rating Scale [CARS] score=36, range=21 to 46). Outcomes assessed included measures of participant skills and behaviors, level of environmental adaption and individualized programming, and family satisfaction with treatment.

One case series⁵⁰ investigated the use of personal digital assistants (PDAs) as memory aids for 22 high school students (age range 14 to 18, mean=16.5) with ASD. While investigators did not report measures of IQ or mental age, participants were all enrolled in a mainstream high school, had home computers, and could operate a PDA independently. Outcomes measured included self-reported performance of activities of daily living. A final case series included 52 self-abusive or aggressive individuals with intellectual disability and ASD living in a residential facility.⁴⁷ Participants ranged in age from 13 to 31 with a median age of 21.6 years and a median IQ among testable individuals of 43 (range 17 to 87). Outcomes measured included the time to exit the residential facility and number of individuals exiting after a fire alarm.

A final case series addressed the transitioning process by assessing effects related to implementing a classroom process—changing classrooms throughout the school day—that individuals would be likely to encounter as they move to high school or college.⁴⁹ The study included 55 individuals with autism attending special school. Adolescent and young adult participants ranged in age from 14 to 22, and the study did not report IQ or language scores. Participants' diagnoses were made by psychologists from the students' home schools prior to entry into the special school.

Detailed Analysis

Adaptive/Life Skills Studies Addressing Independent Functioning

A poor quality RCT⁴⁸ demonstrated challenges related to utilizing highly salient, non-criterion-related prompts (i.e., color coded targets) in teaching a specific shoe lacing skill to a group of 20 young adolescents (mean age 12.3) with significant cognitive limitations (average developmental age of 3.05). Participants were randomized to attempt to lace a shoe with color coded laces and eyelets or a shoe with no color coding. Participants typically mastered the shoe lace task more quickly in the color-coded condition but were not able to complete lacing a non-color coded shoe as quickly, suggesting that participants may have concentrated more fully on the color-coded prompt than the mechanics of the task.

A poor quality prospective case-series demonstrated substantial improvement in success of exiting a facility when an alarm was activated for a group of adults with autism and/or intellectual disability. While only 25 percent achieved the exit at baseline, all participants (100 percent) were able to exit successfully with implementation of a systematic applied behavior analysis-based training protocol.⁴⁷

One poor quality cohort study compared the effects of an experimental treatment setting, a combined residential and vocational TEACCH-based training program model with 3 control conditions: group homes, institutions, or family homes.⁴⁶ The farm-based TEACCH program emphasized farming and landscaping as vocational modalities and focused on teaching skills and ameliorating behavioral problems. All participants were applicants to the TEACCH residential program. Investigators used a part-random, part-clinical/administrative assignment procedure to assign participants, matched on cognitive ability, autism and challenging behavior severity, communication skills, and need for supervision, to the TEACCH treatment group (n=6). The other participants were living in a control setting (group homes, n=10; institutions, n=6; family homes, n=10). Participants were similar at baseline except in the case of individuals in family homes, who were less likely to have experienced residential placement before age 18. The mean age of all participants at baseline was 25 (range=16 to 48 years). Eighty-five percent had severe

to profound intellectual disability (Vineland Adaptive Behavior Composite mean=25), and most had moderate to severe autism (mean CARS score=36, range=21 to 46). A majority of participants (53 percent) had experienced residential treatment prior to age 18.

Research assistants measured outcomes at baseline and 12 months after treatment/residence began for the TEACCH group. Outcomes assessed included measures of participant skills and behaviors, level of environmental adaption and individualized programming, and family satisfaction with treatment. The TEACCH program was rated as employing more communication adaptations, socialization programming, preventive behavior management approaches, and visual structure (all $p < 0.0004$) than the other settings. TEACCH was also rated more highly in terms of desirability of the living situation and use of programming ($P = 0.0001$ for both). Researchers rated group homes as more desirable settings than institutions. Exploratory analyses of changes in skills and behaviors showed variable results with few significant changes in skills or negative behaviors over time across groups.⁴⁶

One poor quality case series⁵⁰ investigated the use of PDAs as memory aids for high school students with ASD. While investigators do not report measures of IQ or mental age, participants were all enrolled in a mainstream high school, had home computers, and could operate a PDA independently. All 22 participants (age range 14 to 18, mean=16.5) reported increases in self-assessed performance of activities of daily living and satisfaction with the PDA after 8 weeks of use following a brief training session ($p < 0.001$). The majority reported independent daily use, and examination of the PDAs showed a variable number of reminders entered. Outcome measures were administered by study investigators who had also provided training in PDA use and included one unvalidated tool.

Table 8. Summary of outcomes of adaptive/life-skills interventions

Author, year, country Groups, N enrollment / N final	Age, mean/ yrs \pm SD IQ, mean \pm SD	Key outcomes
Study quality		
Gentry et al., ⁵⁰ 2010 United States G1: PDA use, 22/22 Quality: Poor	G1: 16.5 (range 14-18) NR	<ul style="list-style-type: none"> Self-rated scores on Canadian Occupational Performance Measure increased from baseline 22/22 participants used PDA daily and reported wanting to continue use; 16/22 could program device independently
Jewell et al., ⁴⁹ 2007 United States G1: Adolescents with rotating classroom schedule, 55/55 Quality: Poor	G1: 17.63 (14-22) NR	<ul style="list-style-type: none"> Rotating classroom schedule (students change classroom throughout the day) had no significant effect on the number of crisis events (baseline mean=2.44 \pm 6.39, followup=2.22 \pm 5.88) or time in crisis (baseline mean minutes=40.27 \pm 102.08, followup=28.96 \pm 65.47)

Table 8. Summary of outcomes of adaptive/life-skills interventions (continued)

Author, year, country Groups, N enrollment / N final	Age, mean/ yrs ± SD IQ, mean ± SD	Key outcomes
Study quality		
Von Bourgondien et al., ⁴⁶ 2003 United States G1: TEACCH-based program, 6/6 G2: Family home, 10/10 G3: Group home, 10/10 G4: Institutions, 6/6	G1: 23.7 ± 4.4 G2: 26.6 ± 5.1 G3: 27.8 ± 8.5 G4: 21.5 ± 5.0 85% of all participants had moderate to severe intellectual disability	<ul style="list-style-type: none"> • Outcomes rated by research assistants • Desirability of living situation and use of programming rated more highly for TEACCH than other conditions; group homes rated more desirable than institutions • Few significant changes in skills or negative behaviors reported in exploratory analyses • Parental satisfaction higher for TEACCH than group homes ($p \leq 0.05$); no difference in parental satisfaction with institutions
Quality: Poor		
Israel et al., ⁴⁷ 1993 United States G1: Facilitated building exit strategies, 52/51	G1: 21.6 (median) (range 13-31) All participants were intellectual disabled	<ul style="list-style-type: none"> • All residents exited building successfully after intensive training with post-training exit times ranging from 48 to 60 seconds
Quality: Poor		
Nelson et al., ⁴⁸ 1980 United States G1: Extra prompts/no extra prompts G2: No extra prompts/extra prompts G1+G2: 20/20	G1: 11.5 ± 3.0 G2: 13.1 ± 4.1 IQ (PEP developmental age) G1: 3.0 ± 0.7 G2: 3.1 v 0.9	<ul style="list-style-type: none"> • G1 completed lacing successfully in mean 108.7 trials plus 81.6 trials with the non-color coded shoe • G2 completed lacing successfully in mean 137.2 trials plus 15.9 trials with the color coded shoe
Quality: Poor		

ASD=autism spectrum disorders; G=group; IQ=intelligence quotient; n=number; NR=not reported; PDA=personal digital assistant; PEP=PsychoEducational Profile; SD=standard deviation; TEACCH=Treatment and Education of Autistic and Communication related Handicapped Children

Adaptive/Life Skills Studies Addressing the Transitioning Process

One poor quality case series⁴⁹ investigated the effect of a rotating classroom schedule (i.e., students change classrooms throughout the day) on behavior warranting crisis intervention among 55 adolescent students at a school for individuals with ASD (mean age=17.63, range 14 to 22). We considered this study as addressing transitional issues because it was intended to examine the effects of a process (classroom changes) that individuals with ASD are likely to encounter as they transition into high school or higher education settings.

The school used crisis management to handle violent, uncontrollable, self-abusive, or dangerous behaviors. Crisis interventions consisted of progressive behavior management techniques that could include restraint as a last resort. Investigators collected data on the number of crisis interventions and time spent in interventions for 6 months prior to and 6 months following the implementation of a rotating classroom schedule. Twenty-two of 55 adolescent participants had crisis events prior to or after the classroom change. The number of crisis events (mean pre-rotation=2.44 ± 6.39, post-rotation=2.22 ± 5.88) and time in crisis were not significantly different across time periods (mean minutes pre-rotation=40.27 ± 102.08, post-rotation=28.96 ± 65.47).

Adaptive/Life Skills Studies Addressing Family Outcomes

The cohort study⁴⁶ investigating a TEACCH-based residential center⁴⁶ also assessed family satisfaction with treatment. Parents were significantly more satisfied with the TEACCH program overall and with individuals' level of community involvement compared with group homes ($p \leq 0.05$), but there was no difference in satisfaction with institutions and either the TEACCH program or group homes. Parents of individuals in the TEACCH residence were also more satisfied with the impact of the placement on the family than parents of individuals in other groups.⁴⁶

Studies of Vocational Interventions

Key Points

- Five poor quality studies assessed vocational interventions for adolescents and young adults with ASD.
- Overall, on-the job supports (broadly defined as services to promote job placement and job retention) may promote employment in the community for young adults with ASD, and community employment may be related to improving quality of life and cognitive performance, as well as an amelioration of autism symptoms.
- Data from a U.S. administrative database reported that the presence of on-the-job supports was related to a higher likelihood of employment in the community (competitive or supported), and that on-the-job supports were as effective in promoting employment for adults with ASD as for adults with other developmental disabilities.

Overview of the Literature

We identified six papers from five unique study populations that addressed the impact of supported employment/vocational interventions on outcomes for adolescents and young adults with ASD (Table 9). One study was a nonrandomized controlled trial conducted in Spain and Germany.^{67, 68} Two prospective cohort studies were conducted in Spain⁶⁵ and the United Kingdom,⁶⁶ and two case series were conducted in the United Kingdom¹² and the United States.¹⁰ All studies were considered poor quality. Appendix G provides the quality ratings for each study.

Interventions addressed in the studies all involved finding and implementing on-the-job supports for young adults with ASD with no other interventions studied. Three of the studies focused on government-funded supports,^{10, 12, 66} and two studies conducted in Spain and/or Germany focused on privately-funded supports.^{65, 67, 68} Three studies included a control group that did not receive the employment/vocational intervention,⁶⁵⁻⁶⁸ and two studies examined the impact of the intervention on employment outcomes without a control group.^{10, 12}

Detailed Analysis

Vocational Studies Addressing Core Symptoms

A poor quality nonrandomized trial reported in two papers^{67, 68} examined the impact of supported employment (community-based jobs with no more than two individuals with ASD in the workplace) versus sheltered workshops (defined as “piece work being performed in

segregated programs with only disabled coworkers”) on autism symptoms⁶⁸ and quality of life⁶⁷ of young adults with ASD (Table 9). Participants were 55 young adults who had received a clinical diagnosis of autism. The study did not report participant recruitment procedures clearly. Investigators assigned 26 participants to a sheltered workshop group and 21 to a supported work group. It is unclear why the sum of number of participants in each group does not match the total sample size.

The average age of participants was 21 years (mean=21.07 ± 4.18, sheltered workshop group; mean=21.64 ± 3.75, supported employment group), and their average IQ scores were in the mid-50s (mean=55.52 ± 14.43, sheltered workshop group; mean=57.41 ± 15.01, supported employment group). There appeared to be more males in the supported employment group (84 percent) than in the sheltered workshop group (69.2 percent), although the study did not assess group differences in gender. Although individuals were matched by gender, autism symptom scores (using the CARS), and IQ, participants were only eligible for the supported employment group if they had an absence of severe behavior problems and acceptable professional and vocational abilities. All of the jobs for those in the supported group were in the community with no more than two individuals with ASD in the same work place. Youth in the supported group worked between 15 to 30 hours a week, were paid competitive wages, and each had a job coach.

The average length of community employment at follow-up was 30 months. Differences between the supported and sheltered workshop groups in autism symptoms or quality of life were not significant before intervention. However, at follow-up, young adults who had participated in the supported work program had reduced autism symptom and higher quality of life scores relative to those who were in a sheltered workshop. Further, the autism symptom differences were due to deterioration in the sheltered group over time, whereas the supported group had no difference in autism symptoms scores from before to after intervention. In contrast, the sheltered workshop group had no difference in quality of life over time, whereas the supported group had quality of life scores that improved from before to after intervention. In sum, these findings suggest that for young adults with autism, supported work in the community may ameliorate increases in autism symptoms and improve quality of life relative to sheltered workshop work.^{67, 68}

A related poor quality prospective cohort study from the same research group⁶⁵ examined the impact of supported employment in the community (supported work group) versus vocational activities in a sheltered setting (no supported work group) on the cognitive development of young adults with autism (Table 9). Participants included 44 young adults (32 men, 12 women) who were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition* (DSM-IV) criteria and who had CARS scores greater than 30. Participants were randomly selected from the Spanish Program of Employment for Autistic People. The mean age of participants was 25.52 years (SD=3.35) for the supported work group and 24.32 (SD=4.34) years for the no supported work group. The average years of schooling was 5.31 (range = 3 to 7 years). The study did not present standardized IQ scores for the participants, but all participants were required to score at about the 35th percentile on the Standard Progressive Matrices, a non-verbal IQ test. Similar to earlier studies,^{67, 68} participants were eligible for the supported work group if they had an absence of severe behavior problems and acceptable professional and vocational abilities. All of the jobs for those in the supported work group were in the community, with no more than two individuals with autism in the same work place. Youth in the supported

work group averaged 20 hours of work a week, were paid competitive wages, and each had a job coach. The average length of community employment at follow-up was 30 months.

The “no supported work” group was on a waiting list for supported work and participated in non-competitive vocational activities during the study period. It is unclear how many participants were in each group. At the start of the study, there were no significant differences between the supported work and no supported work groups in vocabulary (British Picture Vocabulary Scale), IQ (Raven’s matrices), or autism symptoms (CARS). There were also no differences between groups at this time on any of the 12 cognitive performance tasks which measured constructs such as psychomotor speed, spatial recognition memory, and executive functioning (many of the tasks were from the Cambridge Neuropsychological Tests: Automatic Battery). Results suggested that, relative to the control group, the supported employment program was associated with improvements over time in 8 of the 12 measures of cognitive functioning.⁶⁵

Table 9. Key outcomes of vocational studies addressing core symptoms

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
Garcia-Villamizar et al., ⁶⁵ 2007 Spain G1: Supported employment G2: Wait list Overall N: 44/44 Quality: Poor	G1: 25.52 ± 3.35 G2: 24.32 ± 4.34 IQ (Raven): G1: 41.14 ± 4.45 G2: 42.23 ± 5.43	<ul style="list-style-type: none"> Adults with ASD participating in a community work program vs. a waitlisted group who participated in non-competitive (i.e., sheltered) vocational activities Follow-up assessment was approximately 30 months after the start of the intervention Relative to the waitlisted group, the supported employment group experienced improvements over time in 8 of the 12 measures of cognitive functioning
Garcia-Villamizar et al., ^{67, 68} 2000 Spain, Germany G1: Sheltered work, 26/26 G2: Supported work, 25/21 Quality: Poor	G1: 21.07 ± 4.18 G2: 21.64 ± 3.75 IQ (Leiter): G1: 55.52 ± 14.43 G2: 57.41 ± 15.01	<ul style="list-style-type: none"> Adults with ASD participating in a community work program had lower autism symptoms and higher quality of life scores relative to those who were in a sheltered workshop Follow-up assessment was approximately 30 months after the start of the intervention

ASD=autism spectrum disorders; G=group; IQ=intelligence quotient; N=number

Vocational Studies Addressing Independent Functioning

We identified two cohort studies^{12, 66} and one case series¹⁰ examining the impact of employment/vocational interventions on outcomes for adolescents and young adults with ASD (Table 10). We rated all studies as poor quality.

In one cohort study conducted in the United Kingdom, the authors examined the outcome of a 2-year supported employment scheme for high-functioning adults with autism or Asperger syndrome.⁶⁶ Participants in the supported employment scheme included 27 males and 3 females. All participants had a formal diagnosis of autism or Asperger syndrome, a performance or verbal IQ score above 70 (as measured by the Wechsler Adult Intelligence Scale), were actively seeking work and able to travel independently, were capable of eventually maintaining employment with minimal support, and had no psychiatric or physical problems that would adversely affect employment. An additional 20 individuals (all male) who met the study criteria were contacted and enrolled into a no-treatment control group. There were no significant differences between the

supported employment and control groups in age (mean=31.1 years for the supported employment group and 28.0 years for the control group), IQ, or vocabulary (British Picture Vocabulary Test) at the start of the study.

The supported employment scheme included job finding and work preparation, educating potential and existing employers and colleagues about ASD, and on-the-job supports. On-the-job supports included assistance from a support worker with dealing with the social and occupational requirements of a job and education about ASD for employers and work colleagues. The frequency of supports decreased over the study period. Although the total study period covered two years, and average amount of time that individuals were registered with the scheme was 17.03 months (range from 5 to 24 months). Over the 2-year evaluation period, young adults in the supported employment group were significantly more likely to find paid employment than those in the control group (63.3 percent vs. 25 percent), and they spent a greater amount of the study time employed (27.09 percent of time employed for the supported employment group and 12.35 percent of time employed for the control group). For those who were employed, the number of hours worked per week did not differ between the supported work vs. control group, however the supported work group had higher wages per hour on average. There were no significant differences between those who were and were not able to find work in IQ, vocabulary, social understanding, or age. The investigators noted that the most important aspect of their supported work program—and also the most expensive—was the “job finding” aspect, which included many hours of making presentations to, meeting with, and negotiating with potential employers. The authors also noted that funds are rarely available to subsidize the “job finding” component.

This same research group conducted a longer-term follow-up of their supported employment scheme, now titled “Prospects.”¹² This prospective cohort study examined whether the gains in employment made during the first two years of the project⁶⁶ persisted for up to 8 years and with a larger cohort (recruited from three regional sites in the United Kingdom). In addition to the 30 young adults with ASD reported on in the earlier study,⁶⁶ an additional 117 young adults who began receiving services between 2002 and 2003 were added to the cohort. The mean age of individuals added to the cohort was 31.4 years (SD=9.3). All had a clinical diagnosis of autism or Asperger syndrome made by a psychiatrist or psychologist, and this diagnosis was confirmed by using the Autism Diagnostic Interview in 20 percent of cases.

Thirteen of the 19 young adults in the original sample who found employment remained employed 7 to 8 years later. For the young adults who were added since the original cohort, the rate of employment remained high, ranging from 70.5 percent to 54.3 percent (depending on regional site). The majority of employed young adults with ASD (84.7 percent) were generally happy with their job.

The final study that examined the impact of vocational/employment interventions was a retrospective case series conducted in the United States.¹⁰ This study examined the effectiveness of vocational rehabilitative services for adults with ASD compared to adults with other developmental disabilities. The investigators identified 1,707 adults with ASD from national data obtained from the U.S. Department of Education’s Office of Special Education and Rehabilitative Services. Participants with ASD were identified using primary impairment causes for the disability in the vocational rehabilitation dataset. Approximately 73 percent of the sample of adults with ASD was 18 to 25 years of age; 15.5 percent was 25 to 34 years; and 11.1 percent was 35 years of age or older. Eighty-four percent of adults were white, 12.8 percent were black,

and 4.2 percent were of Hispanic ethnicity. As this was an administrative database, data were not available about autism symptoms or cognitive abilities. The study reported that the presence of on-the-job supports (which could include counseling, on-the-job training, job search assistance, assessment and diagnosis, and assistive technology) was related to a higher likelihood of employment in the community (competitive or supported), and that on-the-job supports were just as effective in promoting employment for adults with ASD as for adults with other developmental disabilities.

Table 10. Key outcomes of vocational studies addressing independent functioning

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
Lawer et al., ¹⁰ 2009 United States G1: Vocational rehabilitation service users, 1,707/1,707 United States Quality: Poor	Age, range (%): 18-25 (73.4) 25-34 (15.5) 35-44 (8.1) 45-54 (2.5) 55-65 (0.5) IQ: NR	<ul style="list-style-type: none"> • Presence of on-the job supports was related to a higher likelihood of employment in the community (competitive or supported) for adults with ASD • On-the job supports were as effective in promoting employment for adults with ASD as for adults with other developmental disabilities
Howlin et al., ¹² 2005 United Kingdom G1a: Pilot supported employment program participants (1995-1996), 30/30 G1b: Supported employment program participants (2003-2005), 117/89 Quality: Poor	G1a: 31.1 ± 9.1 G1b: 31.4 ± 9.3 IQ (Raven nonverbal): G1a: 110.2 ± 17.6 G1b: 110.7 v 19.5	<ul style="list-style-type: none"> • For adults in the 8-year follow-up (1995-1996 sample), 13 of 19 (68%) who had been previously employed remained employed • For adults in the additional sample (2003-2005), employment ranged from 70.5% to 54.3%, depending on regional site • No comparison group
Mawhood et al., ⁶⁶ 1999 United Kingdom G1: Supported employment program, 30/30 G2: Control, 20/20 Quality: Poor	G1: 31.1 ± 9.1 G2: 28.0 ± 6.1 IQ (WAIS full scale): G1: 98.8 ± 16.3 G2: 97.7 ± 20.4	<ul style="list-style-type: none"> • 2-year supported employment scheme for high-functioning adults with autism or Asperger syndrome • Adults in the supported work group were more likely to find paid employment (63% vs. 25%) and had higher wages per hour on average than a control group • No differences between groups in number of hours worked per week for those who worked

ASD=autism spectrum disorders; G=group; IQ=intelligence quotient; SD=standard deviation; WAIS=Wechsler Adult Intelligence Scale

Studies of Medical Interventions

Key Points

- Eight studies of pharmacologic agents met our review criteria; four of these were RCTs of fair quality. One additional RCT and three case series were poor quality.

- Little evidence supports the use of medical interventions in the adolescent and young adult population; most studies focused on the use of medications to address specific challenging behaviors.
- Studies of risperidone reported improvements in aggression, irritability/agitation, repetitive behavior, sensory motor behaviors, and overall behavioral symptoms in participants receiving risperidone.
- A placebo-controlled cross-over study reported that haloperidol significantly improved hyperactivity/defiance ratings, but no significant difference was found for irritability/agitation or other symptoms.
- Studies of serotonin reuptake inhibitors (SRIs) had inconsistent results: an RCT of fluvoxamine reported decreases in repetitive behavior, aggression, autistic symptoms, and language usage and case series addressing sertraline, fluoxetine, and clomipramine reported some benefits, while a cross-over study of clomipramine vs. placebo reported no significant differences in autistic symptoms between groups.
- A cross-over study of naltrexone reported no significant improvements in problem behavior and worsening of stereotyped behavior with naltrexone compared with placebo.
- Harms reported across all studies included sedation, weight gain, fatigue, self-injurious behavior, constipation, anxiety, and insomnia.

Overview of the Literature

We identified a total of eight studies of medical interventions.^{42-45, 60-62, 64} All eight of these were studies of pharmacological agents. Overall, no studies were good quality, four were fair quality,⁴²⁻⁴⁵ and four were poor quality.^{60-62, 64} Appendix G provides the quality ratings for each study.

Three RCTs addressed the efficacy of antipsychotic medications (Table 11).^{42, 43, 60} Two were conducted in the United States, and one in Canada. All of these RCTs were conducted in academic clinic settings using institutional and grant funding, and one was fair quality⁴³ and two poor.^{42, 60}

One fair quality RCT was conducted in an academic clinic in the Netherlands and investigated an opiate antagonist (Table 12).⁴⁵ Funding for the study came from institutional and grant sources. Five studies investigated serotonin reuptake inhibitors (SRIs) (Table 13).^{42, 44, 61, 62, 64} Two studies were fair quality,^{42, 44} and the balance were poor.^{61, 62, 64} These studies included two RCTs;^{42, 44} one was conducted in the United States and one in Canada. Three poor quality case series were conducted in the United States.^{61, 62, 64} All five of these studies were conducted in academic clinic settings using institutional and grant funding.

Detailed Analysis

Medical Studies Addressing Comorbidities and Associated Symptoms

We summarize results of studies of medical interventions meeting our criteria below. The Introduction section of the report contains a description of the mechanism of action of these drugs.

Antipsychotics. Three studies addressed the efficacy of antipsychotics (Table 11).^{42, 43, 60} One fair quality RCT⁴³ assessed the efficacy and safety of risperidone in adults with autistic disorder

or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). Inclusion criteria were being an adult, having an Autistic Disorder or PDD-NOS diagnosis based on DSM-IV criteria, and at least “moderate” symptom severity on the Clinical Global Impression of Severity (CGI-S) Scale. Participants had either a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) compulsive subscale score greater than 10, a Self-injurious Behavior Questionnaire (SIB-Q) score of 25 or greater, or a Ritvo-Freeman Real-life Rating Scale overall score of 0.20 or more. Exclusion criteria included a diagnosis of schizophrenia or psychosis, or any significant acute medical condition. The experimental design was a 12-week randomized, double-blind, placebo-controlled phase followed by a 12-week open-label risperidone treatment phase for patients from the placebo group. Subjects were off all psychiatric medications for more than 4 weeks before the trial started.

Risperidone dosing began with 1 milligram (mg) at night and advanced to twice daily dosing, increasing every 3 to 4 days by 1 mg/day, up to a maximal clinical effect or a maximum dose of 10 mg/day. Outcome measures included a modified version of the Y-BOCS, the SIB-Q, the Ritvo-Freeman Real-life Rating Scale, visual analog scales of different mood states, the Clinical Global Impression of Improvement (CGI-I), vital signs, and monitoring for extrapyramidal effects or other adverse effects. Subjects with a CGI-I score of “much improved” or “very much improved” were considered responders. The primary outcomes were global improvement (CGI), repetitive behavior (Y-BOCS), aggression (SIB-Q), and social relatedness (Ritvo-Freeman).

The mean age of the 31 subjects who began the trial was 28.1 years (SD 7.3) and mean full-scale IQ was 54.6 (SD 23.9). Only 24 subjects completed the trial. Fifty seven percent (8 of 14 subjects) were considered responders in the risperidone group, while none (0 of 16 subjects) in the placebo group were responders ($p < 0.002$). Repetitive behavior as measured by Y-BOCS improved over time ($p < 0.001$) for the risperidone group compared with the placebo group at each time point. This result was consistent with improvements over time in the open-label phase ($p < 0.03$). Aggressive behavior as measured by SIB-Q improved over time ($p < 0.001$) for the risperidone group compared to the placebo group. This result was consistent with improvements over time in the open-label phase ($p < 0.05$). Symptomatic improvements as measured by the Ritvo-Freeman for the risperidone group compared to placebo were significant over time for sensory motor ($p < 0.004$), affectual reactions ($p < 0.001$), and overall score ($p < 0.05$); however differences for social relationships, sensory responses, or language were not significant.

These results were consistent with the improvements over time in the open label phase except that sensory responses reached significance in the open label phase. Clinician-rated visual analog scales were significantly decreased in the risperidone group compared with placebo for “anxious or nervous” ($p < 0.02$), “depressed” ($p < 0.03$), and “irritable” ($p < 0.01$); however there were no significant differences for “calm,” “eye contact,” “happy,” “restless,” “social interaction,” “talkative,” or “tired.” Seven subjects did not complete the trial (3 in the risperidone arm and 4 in the placebo arm), with six subjects dropping out due to lack of improvement or agitation, and one subject in the risperidone arm with abnormal gait.

A poor quality cross-over study addressed the safety and efficacy of risperidone in children, adolescents, and adults with intellectual disability.⁶⁰ Inclusion criteria were age 6 to 65 years; a 6-month or longer history of aggression, property destruction, or self-injury; and Aberrant Behavior Checklist-Community (ABC-C) scales above normal range. Exclusion criteria included a history of hypersensitivity to risperidone, neuroleptic malignant syndrome, seizures within the last year, degenerative brain disease, and problematic living/social situation. Subjects were free

of all psychiatric medications for at least 2 weeks prior to entering the trial. The placebo-crossover design began with a placebo run-in phase (3 to 5 weeks). The study randomized participants to low dose risperidone (1 mg/day for children and adolescents, 2 mg/day for adults) or high dose risperidone (0.05 mg/kg/day), divided into a twice-daily schedule. The first treatment period started with 2 weeks of titration followed by 4 weeks at a constant dose. For the second treatment period, subjects crossed over to the other dose with 2 weeks of titration followed by 4 weeks at a constant dose. The cross-over study design changed to an open-label design after a second placebo period (3 to 5 weeks) followed by 24 weeks of unblinded maintenance at the better risperidone dose.

Outcome measures included the ABC-C, the Dyskinesia Identification System Condensed User Scale, the Neuroleptic Side Effects Checklist, routine laboratory tests, and weight. Prolactin, hemoglobin A1c, and lipid profile were measured in a subset of the study subjects (n=20). The primary outcome was the ABC-C Irritability subscale score.

Of the forty subjects, all had intellectual disability, 28 (70 percent) met DSM-IV criteria for autistic disorder, and 8 (20 percent) met DSM-IV criteria for PDD-NOS. The mean age was 22.0 years (SD 13.1). Twenty-three (57.5 percent) of subjects responded fully, and 35 (87.5 percent) had at least a partial response. The study defined a 50 percent reduction in the ABC-C Irritability/Agitation subscale score as a full response and a 25 percent reduction as a partial response. The mean ABC-C Irritability/Agitation subscale score was significantly different for both treatment periods compared to the second placebo period ($p=0.0002$). There was no significant dose effect for the ABC-C Irritability/Agitation subscale between low- and high-dose risperidone ($p=0.13$).

A fair quality crossover study⁴² investigated the efficacy of haloperidol for the treatment of autism. Inclusion criteria were a DSM-IV diagnosis of autism; a recommendation for pharmacotherapy based on initial assessments; and never previously having completed an adequate trial of haloperidol or the SRI clomipramine. Exclusion criteria were not reported. The study design was a double-blind, placebo-controlled, crossover with random assignment to 7-week treatment phases of haloperidol, clomipramine, and placebo. Haloperidol dosing started at 0.25 mg at bedtime and increased in 0.25 mg increments every 2 days until the dose was 0.50 mg twice daily, then further 0.25 mg adjustments were made every 3 to 4 days based on clinical assessment. The dose was reduced to the last dose tolerated if adverse effects were experienced. There was a dosage taper during week 7 of each treatment phase. There were one-week placebo washout periods between each treatment phase. No other psychotropic drugs were allowed except benztropine. Outcome measures included the CARS, the Aberrant Behavior Checklist (ABC), the Dosage Treatment Emergent Symptom Scale, and the Extrapyramidal Symptom Rating Scale.

We summarize results for haloperidol and placebo here and address clomipramine results below (see Serotonin Reuptake Inhibitor section). Of the 37 subjects recruited, 36 (mean age=16.3 years) were included in final analyses. The mean daily dose of haloperidol was 1.3 mg. The mean duration of haloperidol treatment was 5.8 weeks with 23 of 33 (69.7 percent) subjects completing the 7-week treatment phase. Seven of 10 subjects who discontinued had adverse effects (see Harms section below). The mean duration of placebo treatment was 5.4 weeks with 21 of 32 (65.6 percent) subjects completing the 7-week phase; 1 of 9 subjects who discontinued had adverse effects which only included nose bleeds ($n = 1$). The other 8 subjects discontinued due to lack of improvement in symptoms. Haloperidol versus placebo was significant for

reductions in ABC Hyperactivity/Defiance scores ($p < 0.05$), but not for the other ABC subscales. The study did not report statistical comparisons of haloperidol versus placebo for the CARS, Extrapyrimal Symptom Rating Scale, or Dosage Treatment Emergent Symptom Scale. The investigators note that carry-over of effects between treatment phases may have affected results in this crossover design, especially with the short one-week washout. Other comparisons between haloperidol and placebo were not discussed.

Table 11. Key outcomes of studies assessing antipsychotics

Author, year, country Groups, N enrollment / N final Study quality	Mean age, years \pm SD	Mean IQ \pm SD	Outcome measure/ Baseline scores, mean \pm SD	Outcome measure/Post-treatment scores, mean \pm SD
<p>Hellings et al.,⁶⁰ 2006 United States</p> <p>G1+G2: Placebo phase, then dose risperidone, followed by crossover to the other risperidone dose, then another placebo phase</p> <p>Placebo I phase: 3-5 weeks of placebo, n=40</p> <p>Acute Dose phase: G1 Low dose (n=39) or G2 high dose risperidone (n=36)</p> <p>Placebo II phase: 3-5 weeks of placebo, n=33</p> <p>Maintenance phase: Optimal dose risperidone, n=32</p> <p>Quality: Poor</p>	<p>G1+G2: 22 \pm 13.1</p>	<p>NR, 40/40 with intellectual disability</p>	<p>ABC-C Irritability: G1+G2, Placebo I phase: 19.16 \pm 9.96</p> <p>G1+G2, Placebo II phase: 18.23 \pm 12.36</p>	<p>ABC-C Irritability: G1, Low dose acute phase: 11.15 \pm 9.28</p> <p>G2, High dose acute phase: 13.31 \pm 8.92 p = 0.13 G1 vs. G2 p = 0.0002 G1+G2 Acute phase vs. G1+G2 Placebo II</p> <p>Maintenance phase scores only reported graphically</p>
<p>Remington et al.,⁴² 2001 Canada</p> <p>G1: Clomipramine G2: Haloperidol G3: Placebo Overall N: 37/36</p> <p>Quality: Fair</p>	<p>Overall: 16.3 (SD NR)</p>	<p>NR</p>	<p>CARS Overall: 41.8 \pm 7.1</p>	<p>CARS: G1: 37.8 \pm 8.7 G2: 36.7 \pm 6.1 G3: 39.4 \pm 7.0 p<0.05, G2 vs. baseline</p> <p>ABC reported only graphically</p>

Table 11. Key outcomes of studies assessing antipsychotics

Author, year, country Groups, N enrollment / N final Study quality	Mean age, years \pm SD	Mean IQ \pm SD	Outcome measure/ Baseline scores, mean \pm SD	Outcome measure/Post-treatment scores, mean \pm SD
McDougle et al., ⁴³ 1998 United States G1: Risperidone, 15/12 G2: Placebo, 16/12 G2a: Open label risperidone following placebo, n=15 Quality: Fair	G1+G2: 28.1 \pm 7.3	G1+G2: 54.6 \pm 23.9	Y-BOCS, compulsion: G1: 16.5 \pm 3.58 G2: 14.29 \pm 3.50 G2a: 14.27 \pm 2.92 SIB-Q: G1: 47.8 \pm 19.5 G2: 37.7 \pm 11.9 G2a: 32.43 \pm 15.89	Y-BOCS, compulsion: G1: 12.77 \pm 3.63 G2: 14.35 \pm 3.02 p<.001, G1 vs. G2 G2a: 11.47 \pm 3.64 p<0.03, G2a vs. BL SIB-Q: G1: 24.2 \pm 9.5 G2: 32.8 \pm 15.0 p<0.001, G2 vs. G1 G2a: 23.07 \pm 13.45 p<0.05, G2a vs. BL

ABC=Aberrant Behavior Checklist; ABC-I=Aberrant Behavior Checklist-Community Rating Scale-Irritability; ASD=autism spectrum disorders; CARS=Childhood Autism Rating Scale; G=group; IQ=intelligence quotient; n=number; NR=not reported; SD=standard deviation; SIB-Q=Self-Injurious Behavior Questionnaire; Y-BOCS=Yale-Brown Obsessive Compulsive Scale

Opioid receptor antagonists. One study of an opioid receptor antagonist met our review criteria (Table 12).⁴⁵ This fair quality randomized, double blind crossover study tested the efficacy and safety of naltrexone on self-injurious behavior and other autistic symptoms in intellectually disabled adults. Inclusion criteria included a diagnosis using the *Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised* (DSM-III-R) criteria that was agreed upon by two clinicians. The study also required that participants' level of social impairment had to go beyond what was expected by the severity of their intellectual disability, although the details of this determination were not reported. The study also included a subgroup with moderate to high levels of self-injurious behaviors, even though they did not meet criteria for autistic disorder. No exclusion criteria were reported.

Concurrent medications, including antipsychotics, were held stable. The study randomized participants to naltrexone or placebo with a 2-week single-blinded placebo period followed by a single dose of naltrexone (100 mg) with placebo for the remainder of that week. This phase was followed by a 4-week treatment period, a 4-week washout period, and finally a crossover to the second 4-week treatment period. The first cohort received naltrexone 50 mg/day, but the dose for the second cohort was changed to naltrexone 150 mg/day. Outcome measures included the ABC; a clinician-rated checklist individualized to self-injurious behavior, stereotyped, and compulsive behaviors of each subject; the CGI-I scale; direct observation for a subgroup of 11 subjects; and laboratory analyses (liver function tests, plasma beta-endorphin, and plasma cortisol levels). The primary outcome was self-injurious behavior.

Of the thirty-three subjects that participated, 24 had autistic disorder and 9 did not. Participants mean age was 29 years (standard deviation=6), and IQ was not reported. Eleven subjects were taking antipsychotics with the dose held steady during the study. The single dose

had no effect on the clinician-rated questionnaire, direct observation, self-injurious behavior, or plasma beta-endorphins. Plasma cortisol was significantly increased ($p = 0.006$) for naltrexone compared to placebo.

Long-term treatment (4 weeks) with naltrexone resulted in a significant increase in stereotypy as measured by the ABC stereotypy subscale. No changes in any of the other outcome measures were significant. The study did not report comparative statistics, but the CGI scale indicated that placebo was superior to 50 mg/day naltrexone in 12 of 18 subjects. The CGI scale showed that 50 mg/day of naltrexone was better than placebo in only 4 of 18 subjects, while placebo was superior in 12 of 18 subjects. The CGI scale also showed that 150 mg/day of naltrexone was better than placebo in 5 of 14 subjects, while placebo was superior in an equal number of subjects (5 of 14). There were no significant correlations between behavioral changes after the single dose of 100 mg naltrexone and the 4-week treatments with naltrexone (50 mg or 150 mg). Further analyses with groups divided into subjects with concurrent antipsychotic and subjects without did not yield any significant effect for naltrexone versus placebo.

Table 12. Key outcomes of studies assessing opioid receptor antagonists

Author, year, country Groups, N enrollment / N final Study quality	Mean age, years \pm SD	Mean IQ \pm SD	Outcome measure/ Baseline scores, mean \pm SD	Outcome measure/Post-treatment scores, mean \pm SD
Willemsen-Swinkles et al., ⁴⁵ 2005 Netherlands G1+G2: 4 week naltrexone phase for cohorts 1 (50mg daily) and 2 (150mg daily) (ASD patients only) G3+G4: 4 week placebo phase for cohorts 1 and 2 (ASD patients only) Overall N: 33/31 Quality: Fair	Overall: 29 \pm 6.0	NR	ABC Stereotypy G1+G2: 9.7 \pm 4.7 G3+G4: 8.3 \pm 5.2	ABC Stereotypy G1+G2: 10.0 \pm 4.7 G3+G4: 9.0 \pm 4.8 $p = 0.018$, G1+G2 vs. G3+G4

ABC=Aberrant Behavior Checklist; ASD=autism spectrum disorders; G=group; IQ=intelligence quotient; mg=milligrams; n=number; NR=not reported; SD=standard deviation

Serotonin reuptake inhibitors. Five studies focused on SRIs met our criteria (Table 13).^{42, 44, 61, 62, 64} One fair quality RCT⁴⁴ investigated the efficacy of fluvoxamine in adults with autistic disorder. Inclusion criteria were adults with a diagnosis of autistic disorder based on the DSM-III-R. Exclusion criteria were a DSM-III-R diagnosis of schizophrenia, psychotic symptoms, illicit substance abuse within the prior 6 months, “notable” medical conditions, seizure disorder, or pregnancy. Participants were not on any psychotropic medications for at least 6 weeks prior to starting the trial. The study randomized participants to placebo or fluvoxamine. Fluvoxamine was initiated at 50 mg daily and increased 50 mg every 3 to 4 days to maximum clinical response or a maximum dose of 300 mg/day. Outcome measures included the Y-BOCS, the maladaptive

subscales of the Vineland Adaptive Behavior Scales, the Brown Aggression Scale, the CGI-I, and the Ritvo-Freeman Real-Life Rating Scale.

All thirty participants (15 fluvoxamine, 15 placebo) completed the 12-week trial. The mean age was 30.1 years (SD 7.1) for the fluvoxamine group and 30.1 years (SD 8.4) for the placebo group. The mean daily dose was 276.7 mg/day (SD 41.7) for the fluvoxamine group and 283.3 mg/day (SD 36.2) for the placebo group (difference not significant). Global improvement as measured by CGI-I was higher for fluvoxamine compared to placebo ($p < 0.001$). Subjects were classified as responders if the CGI-I scores were “very much improved” or “much improved.” There were significantly more responders ($p < 0.001$) in the fluvoxamine group (8 of 15 subjects) compared to the placebo group (0 of 15). Scores for the fluvoxamine group improved more than those for the placebo group for the Y-BOCS ($p < 0.001$), Vineland maladaptive subscales ($p < 0.001$), Brown Aggression Scale ($p < 0.03$), overall Ritvo-Freeman Scale ($p < 0.04$), and Ritvo-Freeman Scale language usage subscale ($p < 0.008$).

Another fair quality study⁴² used a double-blind, placebo-controlled crossover design to investigate the efficacy of clomipramine and haloperidol for the treatment of autism. Inclusion criteria were a DSM-IV diagnosis of autism; a recommendation for pharmacotherapy based on initial assessments; never previously having completed an adequate trial of haloperidol or clomipramine. Exclusion criteria were not reported. Investigators randomized participants to 7-week treatment phases of haloperidol, clomipramine, and placebo. Clomipramine dosing started at 25 mg at bedtime and increased in 25 mg increments every 2 days until the dose was 50 mg twice daily, then further 25 mg adjustments were made every 3 to 4 days based on clinical assessment. The dose was reduced to the last dose tolerated if adverse effects were experienced. There was a dosage taper during week 7 of each treatment phase and 1-week placebo washout periods between each treatment phase. No other psychotropic drugs were allowed except benztropine. Outcome measures included the CARS, the ABC, the Dosage Treatment Emergent Symptom Scale, and the Extrapyrimal Symptom Rating Scale. Adverse effect outcomes were changes in stereotypy as measured by the Extrapyrimal Symptom Rating Scale and toleration of adverse effects which was measured by continuation of each treatment phase.

We summarize results for clomipramine and placebo here and haloperidol results above (see Antipsychotic section). Of the 37 subjects recruited, 36 (mean age=16.3 years) were included in final analyses. The mean daily dose of clomipramine was 128.4 mg. The mean duration of clomipramine treatment was 4.5 weeks with 12 of 32 (37.5 percent) subjects completing the 7-week treatment phase; 12 of 12 subjects that discontinued had adverse effects (see Harms section below).

The mean duration of placebo treatment was 5.4 weeks with 21 of 32 (65.6 percent) subjects completing the 7-week treatment phase. One of 9 subjects who discontinued had adverse effects which only included nose bleeds ($n = 1$). The study did not report statistical comparisons for clomipramine versus placebo for the CARS, Extrapyrimal Symptom Rating Scale, or Dosage Treatment Emergent Symptom Scale. The study did not report on the effects of clomipramine compared with placebo for ABC subscales. The investigators note that carry-over of effects between treatment phases may have affected results in this crossover design, especially with the short 1 week washout.

One poor quality study⁶² assessed the efficacy and tolerability of clomipramine using a prospective open-label case series design over 12 weeks. The inclusion criterion was a DSM-IV diagnosis of a pervasive developmental disorder (autistic disorder, Asperger disorder, and PDD-

NOS). Subjects were excluded if they had any additional DSM-IV diagnosis other than intellectual disability, had abused illicit drugs within 6 months, were pregnant, or had an acute medical illness. Clomipramine was initially dosed at 50 mg daily, and then increased by 50 mg every 3 to 4 days up to the maximum clinical response or a maximum dose of 250 mg daily. No psychotropic medications were allowed except antiepileptic medication which were held stable and chloral hydrate as needed for agitation. Outcome measures included the Y-BOCS, Brown Aggression Scale, Ritvo-Freeman Real-Life Rating Scale (sensory motor behaviors, social relationship, affectual reactions, sensory responses, and language subscales), and CGI-I. Of the 35 subjects, 33 completed the study and were taking a mean dose of 139 mg (SD 50). There was a significant improvement ($p < 0.001$) in CGI-I global symptoms over time with clomipramine treatment. Of the 33 subjects completing the trial, 18 (55 percent) were responders as determined by CGI score of “very much improved” or “much improved.” Clomipramine treatment significantly reduced ($p < 0.001$) repetitive thoughts and behaviors as measured by Y-BOCS. Aggression as measured by the Brown Aggression Scale significantly decreased ($p < 0.001$) over time with clomipramine treatment. Clomipramine treatment significantly improved ($p < 0.001$) autistic symptoms as measured by the Ritvo-Freeman Scale overall score, as well as all each subscale. The two subjects not completing the trial withdrew due to agitation in one individual and abdominal cramping in the second participant. There was no placebo control group to compare with the clomipramine treatment group in this open-label trial.

Another poor quality, 12 week open-label prospective case series⁶¹ investigated the efficacy and tolerability of sertraline. Inclusion criteria were a DSM-IV diagnosis of autistic disorder, Asperger disorder, or PDD-NOS; a minimum Y-BOCS score (> 15 for verbal subjects, >7 for nonverbal subjects); minimum of score of 0.20 on the Ritvo-Freeman scale, minimum score of 25 on the SIB-Q; and a minimum of 5 on the Vineland Maladaptive Behavior Scale, part 2. Sertraline was initially dosed at 50 mg daily, and then increased by 50 mg every week to a maximum clinical response, maximal dose tolerated, or maximum dose of 200 mg daily. The study allowed no psychotropic medications except chloral hydrate as needed for agitation. Outcome measures included the Y-BOCS, SIB-Q, Ritvo-Freeman Real-Life Rating Scale, and CGI-I. Of the 42 subjects, 37 completed the trial. The mean sertraline dose was 122.0 mg (SD 60.5). Of the 42 subjects starting the trial, 24 (57 percent) were considered responders based on CGI-I score of “very much improved” or “much improved.” Five subjects withdrew from the study: 3 due to anxiety/agitation, 1 due to syncope, 1 due to noncompliance. There was no placebo control group for comparison of possible therapeutic effects or adverse events.

Finally, a poor quality retrospective case series⁶⁴ studied the therapeutic effects and tolerability of fluoxetine and included 23 individuals with ASD (mean age 15.9 ± 6.2). Most participants (21/23) had concomitant intellectual disability. Participants received up to 80 mg/day of fluoxetine for a mean of 189 ± 153 days. CGI ratings of overall clinical severity improved in 15 participants as did ratings of perseverative or compulsive behavior.

Table 13. Key outcomes of studies assessing SRIs

Author, year, country	Mean age, years \pm SD	Mean IQ \pm SD	Outcome measure/ Baseline scores, mean \pm SD	Outcome measure/Post-treatment scores, mean \pm SD
<p>Remington et al.,⁴² 2001 Canada</p> <p>G1: Clomipramine G2: Haloperidol G3: Placebo Overall N: 37/36</p> <p>Quality: Fair</p>	<p>Overall: 16.3 (SD NR)</p>	NR	<p>CARS Overall: 41.8 \pm 7.1</p>	<p>CARS: G1: 37.8 \pm 8.7 G2: 36.7 \pm 6.1 G3: 39.4 \pm 7.0 p<0.05, G2 vs. baseline</p> <p>ABC reported only graphically</p>
<p>McDougle et al.,⁶¹ 1998 United States</p> <p>G1: Sertraline, n=42/37 G1a: AD G1b: AS G1c: PDD NOS</p> <p>Quality: Poor</p>	26.1 \pm 5.8	60.5 \pm 22.7 (28 with intellectual disability)	<p>Y-BOCS, total score: G1a: 16.5 \pm 6.7 G1b: 25.7 \pm 4.1 G1c: 18.2 \pm 4.8</p> <p>Vineland maladaptive behavior: G1a: 27.0 \pm 9.4 G1b: 19.8 \pm 8.6 G1c: 28.3 \pm 10.8</p> <p>SIB-Q: G1a: 32.7 \pm 16.5 G1b: 17.5 \pm 7.7 G1c: 36.2 \pm 16.4</p>	<p>Y-BOCS, total score: G1a: 11.5 \pm 5.8 G1b: 27.8 \pm 5.3 G1c: 14.8 \pm 5.7 p = 0.005, G1 vs. baseline</p> <p>Vineland maladaptive behavior: G1a: 13.8 \pm 6.0 G1b: 20.2 \pm 8.2 G1c: 19.5 \pm 9.1 p = 0.0001, G1 vs. baseline</p> <p>SIB-Q: G1a: 15.5 \pm 9.5 G1b: 18.8 \pm 7.7 G1c: 20.2 \pm 12.8 p = 0.0001, G1 vs. baseline</p>

Table 13. Key outcomes of studies assessing SRIs (continued)

Author, year, country	Mean age, years \pm SD	Mean IQ \pm SD	Outcome measure/ Baseline scores, mean \pm SD	Outcome measure/Post-treatment scores, mean \pm SD
<p>Brodkin et al.,⁶² 1997 United States</p> <p>G1: Clomipramine, 35/33 G1a: Responders, n=18 G1b: Nonresponders, n=15</p> <p>Quality: Poor</p>	G1: 30.2 \pm 7.0	G1: 64.6 \pm 27.2	<p>Y-BOCS, total score: G1a: 18.7 \pm 6.8 G1b: 17.9 \pm 6.2</p> <p>Y-BOCS, compulsion subscale: G1a: 13.7 \pm 3.3 G1b: 13.9 \pm 2.5</p> <p>Y-BOCS, obsession subscale: G1a: 10 \pm 6.8 G1b: 6.7 \pm 6.2</p> <p>Brown Aggression Scale: G1a: 10.6 \pm 7.4 G1b: 6.5 \pm 4.1</p>	<p>Y-BOCS, total score: G1a: 9.1 \pm 3.0 G1b: 17.3 \pm 7.8 P < 0.001, G1 vs. baseline P < 0.001, G1a vs. G1b</p> <p>Y-BOCS, compulsion subscale: G1a: 6.9 \pm 2.1 G1b: 12.5 \pm 3.3 P < 0.001, G1 vs. baseline P < 0.001, G1a vs. G1b</p> <p>Y-BOCS, obsession subscale: G1a: 4.4 \pm 2.8 G1b: 8 \pm 6.6 P < 0.001, G1 vs. baseline P < 0.001, G1a vs. G1b</p> <p>Brown Aggression Scale: G1a: 3.7 \pm 3.6 G1b: 6.4 \pm 4.6 P < 0.001, G1 vs. baseline P < 0.001, G1a vs. G1b</p>
<p>McDougle et al.,⁴⁴ 1996 United States</p> <p>G1: Fluvoxamine, 15/15 G2: Placebo, 15/15</p> <p>Quality: Fair</p>	G1: 30.1 \pm 7.1 G2: 30.1 \pm 8.4	G1: 82.5 \pm 26.8 G2: 77.3 \pm 33.1	<p>Y-BOCS, total score: G1: 21.4 \pm 7.3 G2: 21.5 \pm 6.8</p>	<p>Y-BOCS, total score: G1: 13.7 \pm 9.1 G2: 21.9 \pm 6.7 P < .003, G1 vs. G2</p> <p>Data for Vineland Maladaptive Behavior and Brown Aggression Scale were not reported, although statistically significant improvements were noted.</p>
<p>Cook et al.,⁶⁴ 1992 United States</p> <p>G1: Fluoxetine, 23/23</p> <p>Quality: Poor</p>	15.9 \pm 6.2	NR, 19 with intellectual disability	<p>CGI-S, total: 5.7 \pm 0.8</p> <p>CGI-S, compulsion: 5.5 \pm 1.5</p>	<p>CGI-S, total: 4.9 \pm 1.1 p<0.002, G1 vs. baseline</p> <p>CGI-S, compulsion: 4.7 \pm 1.6 p<0.005, G1 vs. baseline</p>

ABC=Aberrant Behavior Checklist; ABC-I=Aberrant Behavior Checklist-Community Rating Scale-Irritability; CARS=Childhood Autism Rating Scale; CGI-S=Clinical Global Impression-Severity; G=group; n=number; NR=not reported; PDD-NOS=Pervasive Developmental Disorder-Not Otherwise Specified; SIB-Q=Self-Injurious Behavior Questionnaire; SRIs=serotonin reuptake inhibitors; Y-BOCS=Yale-Brown Obsessive Compulsive Scale

Medical Studies Reporting Harms

In one study of risperidone⁴³ the authors describe sedation as the most prominent adverse effect. Seven subjects did not complete the trial (three in the risperidone arm and four in the placebo arm), with six subjects dropping out due to lack of improvement or agitation, and one subject in the risperidone arm with abnormal gait. In another study of risperidone⁶⁰ the most common adverse effects during the risperidone periods of the cross-over phase were sedation and gastrointestinal complaints. In 13 subjects these adverse effects triggered automatic 50 percent dose reductions per the study protocol. The Dyskinesia Identification System Condensed User Scale scores from the treatment phases were not statistically different when compared either to the first placebo period ($p=0.052$) or the second placebo period ($p=0.482$). Symptoms on the Neuroleptic Side Effects Checklist that were the most significant ($p<0.001$) with treatment included drowsiness, weight gain, and increased appetite. Other symptoms were also significant ($p<0.05$) including “too quiet,” “not themselves,” tremor, “lack of spontaneity,” and nasal congestion. Mean weight gain during the entire study was 8.3 kg for adolescents and 6.0 kg for adults. There were no abnormal laboratory tests.

In a study of haloperidol⁶⁹ the mean duration of haloperidol treatment was 5.8 weeks with 23 of 33 (69.7 percent) subjects completing the 7-week treatment phase; seven of 10 subjects who discontinued had adverse effects, including fatigue ($n = 5$), dystonia ($n = 1$), and depression ($n = 1$). The mean duration of placebo treatment was 5.4 weeks with 21 of 32 subjects (65.6 percent) completing the 7-week phase; one of nine subjects who discontinued had adverse effects which only included nose bleeds. The other eight subjects discontinued due to lack of improvement in symptoms. There were no significant changes in 12-lead electrocardiogram variables, either in the haloperidol or placebo phases.

In one study of opioid receptor antagonist identified,⁴⁵ 11 subjects were taking antipsychotics with the dose held steady during the study. Possible adverse events included one subject with an acute increase in self-injurious behavior, one subject with nausea and tiredness, and three subjects with sedation. Liver function tests remained within normal ranges. The single dose had no effect on the clinician-rated questionnaire, direct observation, self-injurious behavior, or plasma beta-endorphins. Plasma cortisol was significantly increased ($p = 0.006$) for naltrexone compared to placebo. Long-term treatment (4 weeks) with naltrexone resulted in a significant increase in stereotypy as measured by the ABC stereotypy subscale.

One study of clomipramine⁴² used a crossover design with a mean duration of clomipramine treatment of 4.5 weeks with 12 of 32 (37.5 percent) subjects completing the 7-week treatment phase; 12 of 12 subjects that discontinued had adverse effects which included fatigue or lethargy ($n = 4$), tremor ($n = 2$), tachycardia ($n = 1$), insomnia ($n = 1$), diaphoresis ($n = 1$), nausea or vomiting ($n = 1$), decreased appetite ($n = 1$), and preexisting right bundle branch block ($n = 1$). The mean duration of placebo treatment was 5.4 weeks with 21 of 32 (65.6 percent) subjects completing the 7-week treatment phase; 1 of 9 subjects that discontinued had adverse effects which only included nose bleeds ($n = 1$). There were no significant changes in 12-lead electrocardiogram variables, either in the clomipramine or placebo arms. Statistical comparisons were not reported for the clomipramine versus placebo for the CARS, Extrapyramidal Symptom Rating Scale, or Dosage Treatment Emergent Symptom Scale.

One study assessing the efficacy and tolerability of clomipramine reported adverse effects in 13 individuals, three of whom had seizures during clomipramine treatment.⁶² Two of the three participants with seizures had previously diagnosed seizure disorders and were concurrently

medicated with antiepileptic medication. The two participants not completing the trial withdrew due to agitation in one individual and abdominal cramping in the second. Other participants who completed the trial experienced constipation (n = 3), weight gain (n = 3), anorgasmia (n = 1), and sedation (n = 2). There were no cardiovascular or extrapyramidal adverse effects. There was no placebo control group to compare with the clomipramine treatment group in this open-label trial.

One RCT⁴⁴ investigated the efficacy of fluvoxamine in adults with autistic disorder. Adverse effects in the fluvoxamine group included mild sedation (n=2) and nausea (n = 3). There were no significant changes in anticholinergic effects, vital signs, routine lab analyses, or electrocardiogram.

In a case series⁶¹ assessing the efficacy and tolerability of sertraline, five subjects withdrew from the study: three due to anxiety/agitation, one due to syncope, one due to noncompliance. There were no cardiovascular, extrapyramidal, or seizure adverse effects. There was no placebo control group for comparison of possible therapeutic effects or adverse events. Finally, another case series⁶⁴ examined fluoxetine and reported that six of 23 participants experienced side effects that “significantly” interfered with function or outweighed therapeutic benefits. Harms reported overall included agitation (n=5), insomnia (n=4), elated affect (n=4), decreased appetite (n=4), and increased screaming (n=2). Additional harms were reported in at least 1 individual (inappropriate behavior, crying, yawning, rash).

Studies of Allied Health Interventions

Key Points

- Five studies, one fair and four poor quality, investigated allied health approaches. Three studies included individuals with ASD and intellectual disability.
- A leisure/recreation program demonstrated positive effects on stress and quality of life.
- Facilitated communication did not increase participants’ communication or literacy abilities over their independent abilities.
- Some positive effects on social skills were reported in studies of music therapy but outcome measures were unvalidated and largely subjective.

Overview of the Literature

We identified five studies of allied health interventions^{41, 51-53, 63} including one fair quality RCT investigating a leisure/recreation program.⁴¹ Appendix G provides the quality ratings for each study. The RCT, conducted in Spain, included 71 individuals ranging from 17 to 49 years of age with mean Leiter mental age scores of 64.36 ± 21.33 months in the intervention group and 61.44 ± 9.37 months in the control group. Assessments included measures of quality of life and stress. Two poor quality prospective case series addressed facilitated communication,^{52, 63} and two poor quality retrospective case series addressed music therapy.^{51, 53} Studies were conducted in the United States⁵¹⁻⁵³ and Canada⁶³ and included participants ranging in age from 2 to 40 across the studies. The duration of treatment ranged from 20 hours to 7 months in three studies;^{52, 53, 63} one study of music therapy reviewed data from participants who had participated in varying hours of therapy.⁵¹ Studies of facilitated communication^{52, 63} employed outcome measures gauging the number of correct responses to a given task with and without the aid of a facilitator. Facilitators helped to steady or physically support the hand of an individual with ASD either typing

responses on a keyboard or pointing to images. Study evaluating a music therapy program^{51,53} reported on the number of goals met and social outcomes or social outcomes using largely subjective measures. Tables 14 and 15 summarize key study outcomes.

Detailed Analysis

Allied Health Studies Addressing Core Symptoms of ASD

Music therapy. A poor quality case series addressing music therapy⁵¹ used 2 years of therapist database records to assess the number of goals met and types of music therapy employed with 40 clients. Participants ages ranged from 2 to 49 years (mean age=13.9) and all had diagnoses on the autism spectrum. Diagnoses were not reported as confirmed within the study. Music therapy involved individual or small or large group sessions and occurred in settings including a community music school or group home. The number of sessions varied for each client.

Therapists assessed each client's "level of difficulty" related to aggression, property destruction, on-task behavior, and other domains on a scale with a maximum value of 14 points (highest level of difficulty); participants' level of difficulty ratings averaged 2.5. Therapists also set and tracked goals met in areas including behavioral/psychosocial skills, language/communication skills, perceptual/motor skills, and cognitive skills. Therapists defined meeting a goal as an increase or decrease of 25 percent from a client's baseline level of performance. Parents also completed annual questionnaires to assess generalizations of skills to other settings. All participants achieved their initial goal within one year as well as achieved 77 percent of intermediate goals. Attainment of goals was not affected by client level of difficulty or session type. Thirty caregivers returned generalization surveys, which reported that all participants used skills practiced in music therapy in non-therapy settings occasionally or frequently.

Facilitated communication. Two poor quality case series addressed facilitated communication,^{52, 63} and included 41 individuals with ASD ranging in age from 8 to 21. Both studies included individuals with limited literacy, and one assessed the effects of facilitated communication via a series of picture recognition tasks performed with and without a facilitator and with the facilitator informed and uninformed of the object presented.⁶³ Facilitators, staff members of a school for individuals with autism, all received 2 days of facilitated communication training. In one task involving participants' pointing to the picture of a word displayed previously, the number of correct responses was greatest when facilitators were aware of the word displayed. Facilitated communication did not enhance participant performance beyond participants' independent communication abilities, and facilitator influence was evident for at least 12 of 20 participants. In a second task using headphones and requiring responses to auditory cues, facilitators heard the same message as participants, a different message, or white noise. Responses across all 3 trials were not significantly different, and facilitator influence was evident for 14/20 participants.

In a third task participants completed segments of the Peabody Picture Vocabulary Test with and without facilitated communication. Scores on the test did not differ significantly between conditions; all 12 participants completing the test showed receptive language difficulties, and there were no clear patterns of facilitator influence. The investigators also collected followup data for 7 participants after 5 to 7 additional months of facilitated communication use. Additional

time with facilitated communication did not increase participants' accuracy of responding and was associated with increased facilitator influence in one task ($p < 0.03$).

A second case series addressing facilitated communication included 21 participants (mean age=15.5) with ASD and mild to profound intellectual disability and language development age equivalent ranging from 1.6 to 5.1 years.⁵² Study tasks involved both facilitated and non-facilitated communication. In the non-facilitated condition, facilitators were screened from stimuli or investigator cues visible or audible to participants. Facilitators were trained in the history and principles of facilitated communication for roughly 4 hours before participating in the study, and facilitators unfamiliar to participants spent at least 2 weeks prior to the study helping participants acclimate. Participants completed baseline measures without facilitation and pre-test measures with the assistance of screened facilitators. These tests were followed by 20 hours of facilitated communication exposure and training prior to completing post-test outcome measures.

Investigators scored participant responses liberally, counting as correct partial words, misspellings, and recognizable character strings embedded in other text (e.g., the characters "OSY" were scored correctly for "yes"). Performance on initial test measures declined from baseline (14/21 participants able to answer some questions correctly) to pre-test (2/21 participants able to answer some questions correctly). At post-test, conducted after facilitated communication training and with screened facilitation, 2 of 21 participants were able to answer some questions correctly. Scores for a test session during which facilitators were not screened were higher, with 6 out of 21 participants able to answer some questions correctly. No participants demonstrated improved communication abilities or literacy.

Table 14. Key outcomes of studies of allied health interventions addressing core symptoms of ASD

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
Music Therapy		
Kaplan et al., ⁵¹ 2005 United States G1: Music therapy, 40/40 Quality: Poor	G1: 13.9 (range 2-49) NR	<ul style="list-style-type: none"> Retrospective review of client database records; music therapists set goals and determined percentage increase/decrease in skills/behavior relevant to goal 40/40 participants with ASD met initial goals within 12 months of therapy; over 70% of participants met intermediate goals All caregivers returning generalization surveys (n=30) reported use of skills practiced in therapy sessions in non-therapy sessions occasionally or frequently

Table 14. Key outcomes of studies of allied health interventions addressing core symptoms of ASD (continued)

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
Facilitated Communication		
Bebko et al., ⁶³ 1996 Canada G1: Facilitated communication Quality: Poor	G1: 13 (range 6-21) G1: 1.3 years - 4 years (mental age range)	<ul style="list-style-type: none"> 6 weeks of FC training and practice with up to 7months followup data for 7 participants Scores on visual stimulus experiment increased from baseline when FC used and facilitator aware of word being prompted (56.86% correct responses vs. 75%); scores decreased from baseline when FC used and facilitator not informed of word prompted (30% correct responses vs.25.57%) Visual stimulus scores increased from baseline when no FC used and facilitator was informed of word being prompted (36.71% correct responses vs. 53.57%) and decreased when no FC used and facilitator not informed of word (35.71% correct vs. 32.57%) FC did not enhance communication beyond participants' independent abilities
Eberlin et al., ⁵² 1993 United States G1: Facilitated communication, 21/21 Quality: Poor	G1: 15.5 (range 11.3-20.2) G1: Mild to moderate intellectual disability, n=2 Moderate to severe intellectual disability, n=11 Severe to profound intellectual disability, n=8	<ul style="list-style-type: none"> 20 total hours FC training Median correct answers declined from baseline (no FC) after testing using FC with facilitator not informed of words prompted (8 correct answers vs. 0); median score at testing with FC and facilitator informed of word prompted=1 Communication ability or literacy did not improve for any participants

ASD=autism spectrum disorders; FC=facilitated communication; G=group; IQ=intelligence quotient; N=number; SD=standard deviation

Allied Health Studies Addressing Independent Functioning

One fair quality RCT investigating a leisure/recreation program randomized individuals with ASD to either a waiting list control group (n=34) or a 12 month leisure program emphasizing engagement in exercise, playing games and completing crafts, interacting with media, and attending social events (n=37) (Table 15).⁴¹ ASD diagnoses were confirmed within the study. Participants ranged in age from 17 to 49 years and had mean Leiter mental age scores of 64.36 ± 21.33 months in the intervention group and 61.44 ± 9.37 months in the control group. Assessments included measures of quality of life and stress completed at baseline and after 12 months by participants with adequate verbal skills or by individuals familiar with the participant. Scores on the stress assessment improved for individuals in the intervention group compared with those in the control group (p<0.001). Overall quality of life scores similarly improved for intervention participants compared with the waiting list group; however, scores on empowerment/independence and social/integration subscales did not improve significantly between groups.

One poor quality case series investigated music therapy interventions using largely subjective measures. One study addressed a university-based program aimed at assessing the feasibility of a music program in promoting social skills in adolescents and young adults with ASD.⁵³ The 22

participants ranged from age 13 to 29 (mean=18), and diagnoses were not reported as confirmed within the study. The program’s curriculum included sessions in learning about music, music appreciation, video production, and storytelling with music over 8 weeks. Investigators assessed participants’ and parents’ impressions of social benefits gained via a 1 (low) to 10 (high) scale and open-ended questions. Both parents and participants rated the program highly with mean scores of nearly 7. Nineteen participants indicated that they had made friends during the program, and 11 parents noted that their children had made friends.

Table 15. Summary of outcomes of studies of allied health interventions addressing independent functioning

Author, year, country Groups, N enrollment / N final Study quality	Age, yrs, mean ± SD IQ, mean ± SD	Key outcomes
Garcia-Villamizar et al., ⁴¹ 2010 Spain G1: Leisure/recreation program, 37/37 G2: Wait list control, 34/34 Quality: Fair	G1: 31.49 ± 4.83 G2: 30.06 ± 3.44 IQ (Leiter) G1: 63.46 ± 21.33 G2: 61.44 ± 9.37	<ul style="list-style-type: none"> • Participants randomized to 12 month recreation/leisure program or waiting list • Stress and total quality of life scores improved for treatment group compared with wait list group (p<0.001) • Scores on empowerment/independence and social/integration subscale improved for treatment group vs. control but not significantly
Greher et al., ⁵³ 2010 United States G1: Music therapy (SoundScape), 22/22 Quality: Poor	G1: 18 (range: 13-29) NR	<ul style="list-style-type: none"> • 8 week program emphasizing understanding elements of music and recording music • Participants and parents rated social benefits of program highly • 11 participants and 19 parents reported that they/their child had developed friendships through the program

G=group; IQ=intelligence quotient; N=number; NR=not reported; SD=standard deviation

Discussion

State of the Literature

Despite a growing population of adolescents and young adults who have diagnoses of an autism spectrum disorder (ASD), almost no research is available to guide therapy in this group. Research to date is scarce, and what is available is lacking in scientific rigor and therefore not suitable to guide practice. We identified a total of 31 studies (one paper reported two separate studies), of which ten were randomized controlled trials (RCTs). Nonetheless, most studies were of poor quality; only five were fair quality and none was good quality.

Studies typically addressed the core symptoms (impairments in communication, social interaction, or behavior) of ASD (Key Question 1) and the effects of interventions on functional and adaptive behavior (Key Question 3). One study addressed the transition process (Key Question 4), and two addressed family outcomes (Key Question 6). Harms of interventions (Key question 5) were only discussed in studies of medical approaches. Similarly, studies of medical approaches addressed Key Question 2, which examined the effects of interventions on comorbid medical or mental health conditions (e.g., epilepsy, sleep disorders, motor impairments, obesity, depression, anxiety, acute and episodic aggression, attention deficit hyperactivity disorder, etc.).

Summary of Outcomes

Studies of Behavioral Interventions

Four poor quality studies of targeted social skills interventions representing group- and computer- based paradigms met our inclusion criteria.^{40, 54-56} Research involving group-based interventions^{54, 55} reported improvements across a variety of social skills as rated by parents and research on computer assisted interventions suggested improvements related to emotion recognition.^{40, 56} However, each study employed a different approach and paradigm, making comparison across interventions impossible. Likewise, such social skills interventions have yet to demonstrate consistent generalization of skills across settings and often circumscribe interventions to individuals with average to above average verbal and/or cognitive abilities. As such, the strength of evidence for social skills interventions is insufficient.

A single poor quality case series of a semi-residential, intensive behavior-based intervention included 34 adolescents and focused on changes in adaptive behavior after 2 years of program attendance.⁵⁷ Overall, both male and female participants improved on measures of socialization, and females also improved in daily living and motor skills. While the authors reported that there was a positive impact across a fairly heterogeneous group, the study did not involve a control group and did not clearly define an intervention; parental satisfaction data reported was positive.

Studies of Educational Interventions

Research into language and communication strategies for adolescents and young adults with ASD is very limited, with only two small crossover studies identified in this population. There is little evidence to support selection among various educational strategies, with one study finding similar vocabulary acquisition between analog and natural language approaches⁵⁹. Procedural

facilitation and anaphoric cuing showed some promise for increasing vocabulary in high-functioning ASD but were addressed in only one small, short term study.⁵⁸

Studies of Adaptive/Life Skills Interventions

Studies of adaptive-focused interventions meeting our criteria were of poor quality, addressed disparate interventions, and included few participants. No study included more than 36 individuals with ASD, and most had concomitant intellectual disability. Interventions addressing teaching self-care skills (shoe lacing, building exiting),^{47, 48} digital memory aids,⁵⁰ and a residential, Treatment and Education of Autistic and Communication related handicapped Children (TEACCH)-based program⁴⁶ reported some positive effects. Studies were typically uncontrolled and of short duration, however.

One poor quality study assessed the effects of a classroom rotation schedule on crisis events in a residential school⁴⁹ and reported no significant increase in events after the implementation of classroom rotation. The few studies addressing family-focused outcomes reported parent or family satisfaction with treatment approaches. One study of a TEACCH-based residential program compared with group homes and institutions reported greater satisfaction with treatment and program participants' community involvement among parents of individuals in the TEACCH-based facility compared with group homes.⁴⁶ Parents of individuals in the TEACCH residence were also more satisfied with the impact of the placement on the family than parents of individuals in other groups. Assignment to the TEACCH program, however, was not random; thus individuals in the group may have differed meaningfully from individuals in group homes, family homes, or institutions.

Studies of Vocational Interventions

Our search identified five studies focused on supported employment/vocational interventions.^{10, 12, 65-68} It is important to note that all of the identified studies focused on on-the-job supports as the employment/vocational intervention; no other vocational interventions were reported in the literature meeting our study criteria. Our ability to assess the benefit of supported employment programs is limited, given the existing research. No study utilized random assignment, making it difficult to draw conclusions about the effectiveness of the programs. In this very limited literature, the clearest benefit of supported employment interventions appears to be in increasing rates of employment for young adults with ASD, with three of the studies focused on employment as the outcome of interest.^{10, 12, 66} There is less evidence of the importance of supported employment interventions in other domains, with studies suggesting that supported employment was associated with improvements in quality of life,⁶⁷ cognitive functioning,⁶⁵ and ameliorated increasing autism symptoms,⁶⁸ relative to young adults with ASD in sheltered work settings.

Supported employment interventions remain understudied. For example, only one study examined rates of employment for programs that lasted 3 years or longer.¹² Further, this longer-term study did not include a control group, making it impossible to determine the rates of employment over time for young adults with ASD who were not participating in the supported employment intervention. Finally, none of the studies examined whether increased employment rates or improvements in other outcomes were sustained after the termination of the supported employment intervention.

In sum, the evidence base suggests that on the job supports may have the potential to promote employment in the community for young adults with ASD, and researchers report that community employment is related to improving quality of life and cognitive performance, as well as an amelioration of the increasingly severe autism symptoms among young adults primarily in sheltered workshop settings. However, the poor quality of the studies renders the conclusions unreliable at this time; they should therefore be taken as potential areas for future research rather than evidence of effectiveness.

Studies of Medical Interventions

The use of medical interventions in adolescents and young adults with ASD is common.⁷⁰ However, there is little evidence that supports the use of medical interventions specifically in this population. We identified three studies of antipsychotic medications,^{42, 43, 60} five studies of serotonin reuptake inhibitors (SRIs),^{42, 44, 61, 62, 64} and one study of an opiate antagonist.⁴⁵ Overall, most of these studies focused on the use of medications to address specific challenging behaviors (i.e., aggression or irritability). Four studies were fair quality,⁴²⁻⁴⁵ and five were poor.⁶⁰⁻⁶⁴

The most consistent findings were identified for antipsychotic medications. An RCT studying risperidone found improvements in aggression, repetitive behavior, sensory motor behaviors, and overall behavioral symptoms.⁴³ A cross-over study of risperidone also showed a significant reduction of irritability/agitation ratings with risperidone treatment, but the control was indirect.⁶⁰ A placebo-controlled cross-over study found that haloperidol significantly improved hyperactivity/defiance ratings, but no significant difference was found for irritability/agitation or other symptoms.⁴² While limited literature supports the use of risperidone in adolescents or young adults with ASD, the efficacy of risperidone in children has moderate strength of evidence²⁵ that is consistent with the results of the one fair RCT and one poor cross-over study in adults with ASD. There is therefore no evidence to suggest that the effects of risperidone for irritability/agitation in ASD is specific to a particular age range.

A number of studies of SRIs were identified but with little consistency across studies. An RCT of fluvoxamine showed decreases in repetitive behavior, aggression, autistic symptoms, and language usage.⁴⁴ In contrast, no significant differences were observed in a cross-over study of clomipramine versus placebo.⁴² Three case series of SRIs were also identified, including sertraline, fluoxetine, and clomipramine, with each study reporting some benefit to treatment.^{61, 62, 64} A cross-over study of the opioid receptor antagonist naltrexone found no significant improvements in problem behavior and showed worsening of stereotyped behavior with naltrexone treatment compared to placebo.⁴⁵

Based upon the published studies in adolescents and adults with ASD, the strength of evidence is insufficient for harms associated with medications tested in this population. As in the case of efficacy, the data on adverse effects associated with risperidone, including sedation and weight gain, are consistent with the strong strength of evidence for these adverse effects in children with ASD.²⁵ There is therefore no evidence to suggest that the adverse effects of risperidone in ASD are limited to a particular age range. Of course, this does not mean that other medications tested in ASD are free of adverse effects. It is reasonable to expect that, in contrast to efficacy, which is more likely to be specific to disorder and symptom, adverse effects are more likely to extend across diverse groups of subjects studied. Clinicians evaluating the evidence and sharing information with families routinely take this perspective, as does the Food and Drug

Administration in mandating that all adverse events be listed for a drug, rather than just those for a particular indication.

As one example, the limited studies of adults with ASD treated with risperidone indicate weight gain as an adverse effect but in too few studies to draw a clear conclusion about the strength of evidence. There is, however, high strength of evidence for weight gain in children with ASD treated with risperidone, as noted in a previous comparative effectiveness review.²⁵ Similarly, recent Cochrane reviews found substantial evidence for weight gain in adults with schizophrenia or bipolar disorder treated with risperidone.^{71, 72} When the broader evidence base is considered, the consistency of these findings supports an association of weight gain with risperidone in adults with ASD, just as is true in children with ASD and adults with other disorders. This approach to assessing the evidence for harms is outside of the scope of this review, but similar conclusions could be drawn with respect to sedation and extrapyramidal symptoms with risperidone or haloperidol.

Studies of Allied Health Interventions

Few studies of allied health interventions met our criteria.^{41, 51-53, 63} One fair quality RCT assessed a 12-month recreation program⁴¹ and reported improved quality of life and lower stress scores in individuals participating in the leisure/recreation program compared with those on a waiting list. One poor quality case series⁵³ included 22 young adults engaged in a music therapy intervention. Nearly all participants reported making friends during the program and were generally satisfied with the program. Both studies assessed outcomes shortly after treatment, so longer-term effects of the interventions are not known.

Two studies of facilitated communication^{52, 63} used approaches designed to assess the effects of facilitation both with and without facilitators' awareness of the word being prompted. Both studies demonstrated some facilitator influence and limited effects on participants' independent ability to communicate. One retrospective study of a music therapy program reported some positive effects on participants' social skills using largely subjective outcome measures.⁵¹

Strength of the Evidence for Effectiveness of Therapies

Overview

We assessed the literature 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 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 have shown 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. Future research may find that the intervention is either effective or ineffective.

Methods for applying strength of evidence assessments are established in the Evidence-based Practice Centers' (EPCs) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*³⁹ and are based on consideration of four domains: risk of bias, consistency in direction

of the effect, directness in measuring intended outcomes, and precision of effect. Table 3 in the Methods section of the report includes a description of these domains.

We determined the strength of evidence for outcomes including social skills, adaptive behavior, autism symptom, challenging and repetitive behavior, harms of treatment, employment, and parent satisfaction. Tables 14 through 19 document the strength of evidence for each domain of the major intervention-outcome combinations.

Strength of the Evidence

Behavioral Interventions

All studies assessing behavioral interventions were poor quality. The strength of the evidence for all interventions targeting social skills is insufficient as it is for an intensive behavioral intervention (Table 16).

Table 16. Intervention, strength of evidence domains, and strength of evidence for outcomes of behavioral studies

Intervention	Study type(N studies of type reporting outcome)	Domains pertaining to Strength of Evidence (SOE):				SOE
		Risk of Bias	Consistency	Directness	Precision	
Adaptive behavior						
Intensive behavioral treatment	Case series (1) ⁵⁷	High	Unknown	Direct	Imprecise	Insufficient
Social skills/social behaviors						
Social Skills Groups	RCT (1) ⁵⁴ Case series (1) ⁵⁵	High	Consistent	Direct	Imprecise	Insufficient
Computer-based intervention ^a	RCT (3) ^{40, 56} nRCT (1) ⁴⁰	Medium	Inconsistent	Indirect	Imprecise	Insufficient
Parent satisfaction						
Intensive behavioral treatment	Case series (1) ⁵⁷	High	Unknown	Direct	Imprecise	Insufficient

^aPaper includes 2 unique studies reported in one publication.

N=number; RCT=randomized controlled trial; SOE=strength of evidence

Educational Interventions

Only two poor quality studies investigated educational interventions targeting communication skills thus we assessed the strength of the evidence as insufficient (Table 17).

Table 17. Intervention, strength of evidence domains, and strength of evidence for key outcomes of educational studies

Outcome/Intervention	Study type (N studies of type reporting outcome)	Domains pertaining to Strength of Evidence (SOE):				SOE
		Risk of Bias	Consistency	Directness	Precision	
Language/communication						
Teaching strategies	RCT (1) ⁵⁸ nRCT (1) ⁵⁹	High	Inconsistent	Direct	Imprecise	Insufficient

N=number; nRCT=nonrandomized controlled trial; RCT=randomized controlled trial; SOE=strength of evidence

Adaptive/Life Skills Interventions

With five poor quality studies targeting disparate outcomes using disparate adaptive/life skills-focused interventions focused on highly specific tasks/skills, we rated the strength of the evidence overall as insufficient (Table 18).

Table 18. Intervention, strength of evidence domains, and strength of evidence for outcomes of adaptive/life skills studies

Intervention	Study type(N studies of type reporting outcome)	Domains pertaining to Strength of Evidence (SOE):				SOE
		Risk of Bias	Consistency	Directness	Precision	
Adaptive/functional behavior						
Self-care/ADL training	RCT (1) ⁴⁸ Prospective cohort (1) ⁴⁶ Case series (3) ^{47, 49, 50}	High	Consistent	Direct	Imprecise	Insufficient
Parent satisfaction						
TEACCH-based program	Prospective cohort (1) ⁴⁶	High	Unknown	Direct	Imprecise	Insufficient

ADL=activities of daily living; N=number; RCT=randomized controlled trial; SOE=strength of evidence; TEACCH=Treatment and Education of Autistic and Communication related Handicapped Children

Vocational Interventions

Five studies assessed employment-related outcomes as well as outcomes related to cognition and autism symptoms. All studies were poor quality, and we assessed the strength of the evidence as insufficient for all outcomes (Table 19).

Table 19. Intervention, strength of evidence domains, and strength of evidence for supported employment/vocational interventions

Intervention	Domains pertaining to Strength of Evidence (SOE):					SOE
	Study type (N studies of type reporting outcome)	Risk of Bias	Consistency	Directness	Precision	
Employment						
Supported employment/ vocational	Case series (2) ^{10, 12} Prospective cohort (1) ⁶⁶	High	Consistent	Direct	Imprecise	Insufficient
Autism symptoms						
Supported employment/ vocational	nRCT (1) ^{67, 68}	High	Unknown	Direct	Imprecise	Insufficient
Quality of life						
Supported employment/ vocational	nRCT (1) ^{67, 68}	High	Unknown	Direct	Imprecise	Insufficient
Cognitive development						
Supported employment/ vocational	nRCT (1) ⁶⁵ Prospective cohort	High	Unknown	Direct	Imprecise	Insufficient

N=number; nRCT=nonrandomized controlled trial; SOE=strength of evidence

Medical Interventions

There were no good studies identified for antipsychotics, serotonin reuptake inhibitors, or opioid receptor antagonists in adolescents or young adults with ASD. The strength of evidence for each of these medication classes is insufficient. Similarly the strength of evidence for adverse effects is also insufficient (Table 20).

The strength of evidence for the use of risperidone to treat irritability and repetitive behaviors in ASD is insufficient based on a single fair RCT⁴³ and a single poor cross-over study⁶⁰. The strength of evidence for the use of haloperidol to treat hyperactivity/defiance in ASD is insufficient based on a single fair study.⁴² The strength of evidence for the use of naltrexone for the treatment of either problem behaviors or core ASD symptoms is insufficient based on a single fair cross-over trial. The strength of evidence for the use of clomipramine for the treatment of ASD symptoms is insufficient based on a single fair study,⁴² and a single poor case series study.⁶² The strength of evidence for the use of fluvoxamine for repetitive behaviors, aggression, or other ASD symptoms is insufficient based on a single fair RCT.⁴⁴

Table 20. Intervention, strength of evidence domains, and strength of evidence for outcomes of medical studies

Outcome/Intervention	Domains pertaining to Strength of Evidence (SOE):					SOE
	Study type (N studies of type reporting outcome)	Risk of Bias	Consistency	Directness	Precision	
Challenging behavior						
Risperidone	RCT (2) ^{43, 60}	Medium	Consistent	Direct	Imprecise	Insufficient
Haloperidol	RCT (1) ⁴²	Medium	Unknown	Direct	Imprecise	Insufficient
Clomipramine	RCT (1) ⁴²	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Case series (1) ⁶²					
Fluvoxamine	RCT (1) ⁴⁴	Medium	Unknown	Direct	Imprecise	Insufficient
Sertraline	Case series (1) ⁶¹	High	Unknown	Direct	Imprecise	Insufficient
Repetitive Behavior						
Risperidone	RCT (1) ⁴³	Medium	Consistent	Direct	Imprecise	Insufficient
Naltrexone	RCT (1) ⁴⁵	Medium	Unknown	Direct	Imprecise	Insufficient
Haloperidol	RCT (1) ⁴²	Medium	Unknown	Direct	Imprecise	Insufficient
Clomipramine	RCT (1) ⁴²	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Case series (1) ⁶²					
Sertraline	Case series (1) ⁶¹	High	Unknown	Direct	Imprecise	Insufficient
Fluoxetine	Case series (1) ⁶⁴	High	Unknown	Indirect	Imprecise	Insufficient
Harms						
Risperidone	RCT (2) ^{43, 60}	Medium	Consistent	Direct	Imprecise	Insufficient
Naltrexone	RCT (1) ⁴⁵	Medium	Unknown	Direct	Imprecise	Insufficient
Haloperidol	Case series (1) ⁶¹	Medium	Unknown	Direct	Imprecise	Insufficient
Clomipramine	RCT (1) ⁴²	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Case series (1) ⁶²					
Sertraline	Case series (1) ⁶¹	High	Unknown	Direct	Imprecise	Insufficient
Fluoxetine	Case series (1) ⁶⁴	High	Unknown	Indirect	Imprecise	Insufficient
Fluvoxamine	RCT (1) ⁴⁴	Medium	Unknown	Direct	Imprecise	Insufficient

N=number; RCT=randomized controlled trial; SOE=strength of evidence

Allied Health Interventions

With only one fair quality RCT of a leisure program addressing quality of life outcomes, we rated the strength of the evidence as insufficient for this outcome. Similarly, the strength of the evidence was insufficient for other allied health interventions and outcomes (Table 21).

Table 21. Intervention, strength of evidence domains, and strength of evidence for outcomes of allied health studies

Intervention	Study type(N studies of type reporting outcome)	Domains pertaining to Strength of Evidence (SOE):				SOE
		Risk of Bias	Consistency	Directness	Precision	
Quality of life						
Recreation program	RCT (1) ⁴¹	High	Unknown	Direct	Imprecise	Insufficient
Social skills/social behaviors						
Music therapy	Case series (1) ⁵³	High	Unknown	Indirect	Imprecise	Insufficient
Language						
Music therapy	Case series (1) ⁵¹	High	Unknown	Indirect	Imprecise	Insufficient
Facilitated communication	Case series (2) ^{52, 63}	High	Consistent	Direct	Imprecise	Insufficient

N=number; RCT=randomized controlled trial; SOE=strength of evidence

Applicability

Applicability of the Evidence

By definition, ASDs are heterogeneous. Characterizing a “typical” individual with an ASD is not possible, although certain symptoms are central to the range of individuals within the autism spectrum. Individual therapies are developed and tested to ameliorate specific symptoms or groups of symptoms, often in a fairly circumscribed subset of children. We describe the applicability of the evidence for interventions represented in this review below.

Behavioral Interventions

Studies of behavioral interventions to date have been limited in scope. The single investigation of an intensive, comprehensive behavioral intervention was conducted across a broad age range of individuals (4 to 18) within a residential rehabilitation center. While numerous studies of younger children have focused on intensive behavioral and developmental interventions, quite often behavioral interventions for adolescents and young adults with ASD have been limited to social skills interventions. Social skills interventions in turn have been limited to investigations conducted with individuals with substantial cognitive and verbal abilities, often individuals with high-functioning autism or Asperger syndrome. Therefore the evidence of social skills interventions is likely applicable only to older, higher functioning individuals. The range of approaches studied also does not always match what is available in practice—that is, either the studies were conducted in highly controlled environments (e.g., university-supported manualized intervention trials), the actual methodology was not well described (i.e., approaches lacking treatment manuals), or the computer based intervention is not widely available. Thus, individuals wishing to infer the potential results of clinical practice based on the available research need to assess carefully the degree to which the study methods matched those available and used in practice. Ultimately, the effectiveness of social skills interventions within and outside of these limited samples and setting is currently unknown.

Educational Interventions

The two studies of educational interventions included in this review were conducted in the United States and Canada in the home and educational environments. Characteristics of participants in the studies (intelligence quotient [IQ], language skills) likely represented a wide spectrum and were not categorized well enough to assess their applicability to the larger population. Educational approaches targeted acquisition of vocabulary and included individual- and group-based strategies; the intensity of interventions varied from a single session to multiple sessions across several weeks. Outcomes examined in this literature primarily focused on reading comprehension and acquisition of vocabulary among individuals exposed to various teaching approaches.

Adaptive/Life Skills Interventions

Several adaptive/life skills studies explicitly included individuals with ASD and intellectual disability,⁴⁶⁻⁴⁸ however specific measures of developmental and behavioral profiles of included individuals were quite variable and often lacked adequate description across studies. One study explicitly included high school students able to use a computer and program a digital device⁵⁰, but specific cognitive and behavioral characteristics of this group were not well described. The remaining study included individuals attending a special school and likewise did not report explicit standardized measurements of the developmental and behavioral characteristics of the group apart from ASD diagnosis.⁴⁹

Studies of certain adaptive/life skills interventions based on intensive application of highly specified programs focused on individuals with ASD with profound cognitive impairments, while specific technological and educational structure-related interventions targeted individuals with cognitive abilities closer to developmental expectations. However, given the variability and limited information concerning developmental, cognitive, and behavioral characteristics of study populations in this category, it is unclear how findings from these studies might apply across varying individuals with ASD. Furthermore, given methodological limitations in study design and time frame, it is not only unclear how adaptive/life skills interventions apply to varying groups of individuals, but it is unclear whether they represent intervention enhancements with meaningful effect over time.

Vocational Interventions

Although often not well characterized, the populations from studies examining the efficacy of supported employment/vocational interventions likely represent higher-functioning adults with ASD. Studies were conducted in the United States, United Kingdom, Spain, and Germany, and two specifically targeted adults with high-functioning autism or Asperger syndrome. One study included those who had nonverbal IQ scores above the 35th percentile. Although a fourth study included adults with a range of intellectual functioning, all adults were required to have “acceptable professional and vocational abilities.” The final study did not report on the intellectual functioning of the sample.

Supported work interventions ranged in duration from 2 years to 8 years, and included job finding services and job coaches who accompanied adults with ASD to the worksite. Comparators included adults in a sheltered work setting (i.e., sheltered workshop) as well as adults who were receiving no supported employment services. The most common outcome assessed was the presence/absence of a job in the community. Other aspects of employment that

were sometimes examined included the length of time employed, number of hours working per week, and wages. One study each assessed autism symptoms, quality of life, and cognitive functioning. Overall, participants in these studies were drawn from the community and thus reflect characteristics of the larger population of higher functioning individuals. Interventions also took place within the larger community. Jobs located were typically support or service positions and do not reflect the scope of employment possibilities potentially available for individuals with ASD with more developed cognitive abilities or social and communication skills.

Medical Interventions

Studies of Antipsychotics

Three RCTs, including mostly adolescents and young adults (age 13 to 30 years) but not limited to this range, examined antipsychotics. Although the mean age was within this range the populations include younger children and older adults. All of the studies used *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition* (DSM-IV) criteria-based diagnoses of autistic disorder as an inclusion criterion. One risperidone study also included individuals with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). Inclusion criteria for the two risperidone studies also included a minimum level of problem behaviors. The mean IQ of the patients was in the range of intellectual disability in the two risperidone studies, while the haloperidol study did not report IQ. Doses of risperidone or haloperidol in all three RCTs were within the range of doses used clinically for some adolescents and young adults with ASD.

All three RCTs assessed aggressive behavior, repetitive behaviors, and general autism symptoms. All of the studies monitored for adverse effects (extrapyramidal and others) either clinically or with specific assessments. Some, but not all, of the studies specifically assessed repetitive behaviors, self-injurious behavior, social relationships, or language. All three of these RCTs were conducted in academic clinic settings in the United States and Canada. The characteristics of these settings may limit applicability.

Studies of Opioid Receptor Antagonists

One placebo-controlled RCT assessed naltrexone and included adult subjects with *Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised* (DSM-III-R) criteria-based diagnoses of autistic disorder. Participants also reportedly had intellectual disabilities. Naltrexone dose in one cohort was 50 mg/day but in the second cohort was increased to 150 mg/day. The increased dose was slightly higher than other studies cited, and the clinical applicability of these doses to patients with ASD has not been established.

The primary outcome was self-injurious behavior. Additional outcomes included irritability, stereotypy, hyperactivity, inappropriate speech, social withdrawal, and global clinical improvement. This RCT was conducted in an academic clinic setting in the Netherlands, and the applicability may be limited by this setting.

Studies of SRIs

Five studies (two placebo-controlled RCTs and four case series) investigated SRIs including clomipramine, fluvoxamine, sertraline, and fluoxetine. All participants had DSM-IV or DSM-III-R criteria-based diagnoses of autistic disorder. Two of studies also included other types of ASD

(e.g., PDD-NOS and Asperger syndrome). Most of the subjects in these studies were adolescents and young adults (ages 13 to 30 years). The mean age was within this range, although some younger children and older adults were included. Drug dosages used in these studies were consistent with doses used clinically for some adolescents and young adults; however, the clinical applicability of these doses to patients with ASD has not been established.

Most of the studies assessed repetitive behaviors, aggressive behavior, and general autism symptoms. Some, but not all of the studies specifically assessed self-injurious behavior, social relationships, or language. All studies were conducted in academic clinic settings in the United States and Canada. The applicability of these studies may be limited by these settings.

Allied Health Interventions

The five studies^{41, 51-53, 63} of allied health interventions meeting our criteria included disparate groups of individuals and interventions. Three of the studies explicitly included individuals with intellectual disability,^{41, 52, 63} and participant ages ranged widely, though most were in the adolescent range. With the exception of an RCT of a recreation program⁴¹ employing a waiting list control condition, studies were case series and thus lacked comparison groups. In studies of facilitated communication, all participants engaged in communication trials in which the facilitator was either aware or not aware of the word or image being prompted. Outcomes included quality of life and stress level in the recreation program RCT, social skills-related outcomes in studies of music therapy, and language/vocabulary in studies of facilitated communication. Interventions occurred in university-based or specialized developmental disabilities treatment centers and may not be widely available to the larger community with ASD. Studies were short term with the exception of the recreation program RCT,⁴¹ which assessed individuals after 12 months of participation.

Gaps in the Evidence

Methodologic Considerations

A number of methodologic considerations may be helpful for understanding the current state of the literature and for guiding future research. Of the 31 studies included in the report, 17 used a comparison group. The rest were case series. Of those, 10 applied random assignment, and of those 10, three were assessed to have randomized appropriately.

Growth in the number of studies with greater attention to rigorous design for the purpose of studying effectiveness will provide additional information for those making decisions about care in the future. About half (17 of 31) of the studies reported use of an adequate diagnostic approach, and we suggest that future research attend to improved reporting about the basis for diagnosis of individuals included in the studies. Most, but not all (25 of 31) fully described inclusion and exclusion criteria, which is helpful for characterizing the population and assessing the applicability of the evidence. Reporting of either fidelity (for behavioral studies) or treatment adherence was low, with seven behavioral studies reporting fidelity and five studies reporting adherence. Again, this information is important to end users of the research for assessing applicability and understanding the implications of the results.

Methodologic strengths in this literature included the use of valid outcomes measures (28 of 31 studies), appropriate sources (e.g., teacher or parent report) of outcome data (30 of 31 studies) and appropriate statistical analysis (25 of 31) for the study design.

Future Research

The period of development representing the transition from adolescence to early adulthood presents numerous challenges for individuals with and without neurodevelopmental challenges. During this same interval individuals with ASD are presented with additional complexities that require efforts to maximize the possibility of a positive transition and achievement of individual goals for independence. Nonetheless, and despite increasing numbers of adolescents facing this transition, no area of research provides sufficient strength of evidence for the impact of specific intervention strategies in terms of improving important outcomes for specific groups of individuals with ASD.

Overall, there is a dearth of evidence in all areas of care for adolescents and young adults with autism spectrum disorders and it is urgent that more rigorous studies be developed and conducted. The lack of randomized, controlled trials is notable in all categories of intervention, but especially so in medical interventions, where substantial adverse events may be associated with medication use in adolescence. Only three studies reported more than 12 months of followup^{12, 46, 67}; longer term data are needed in all areas of therapy.

The behavioral literature generally focuses on subsets of individuals with ASD; often those who are higher functioning, and may not be representative of the range of individuals with ASD. In particular, more attention is warranted to understanding the impact of behavioral interventions in the lives of individuals and how these interventions generalize to real-world impact and outcome. Few studies addressing educational interventions in the adolescent and young adult population have been conducted, and studies focusing on life skills or adaptive behaviors have included few individuals in typically short-term studies focused on very specific short-term intermediate outcomes. More research in both areas over a broader time frame with more clearly defined populations is critical for helping individuals with ASD transition to greater independence.

In vocational research, studies are needed that illuminate which aspects of multifaceted supported employment programs have the greatest impact. Studies that do show evidence of effectiveness in this area should collect longer-term data to describe the degree to which findings, including the duration of employment, continue after the intervention itself is removed. These studies should also broaden the outcomes measured, to include other functional outcomes such as quality of life, educational attainment, residential outcomes and social outcomes. Similarly, allied health studies are needed to understand best approaches to fostering independent living skills.

Medical studies conducted in adolescents and young adults have focused largely on problem behaviors. Clear evidence supports the use of risperidone and aripiprazole in children with ASD. The only fair quality study of risperidone in adults is consistent with the findings in children, but no the strength of evidence based upon the adult literature alone is insufficient to draw firm conclusions. Population studies may be helpful to empirically group ASD patients by age in a way that fosters more effective studies of treatments. Understanding the age-appropriateness of potential medical treatments as based on social, physiological, pharmacological, and functional characteristics of the population would help to prioritize future research. Increased use of such

standardized age groupings would facilitate comparisons of effectiveness within medical intervention categories as well as with non-medical therapies.

Thus far, medication research in adolescents and young adults with ASD has been limited to compounds that are already approved for other indications. As targeted treatments for ASD emerge, initial studies will need to study adult populations to establish safety before moving into studies of adolescents and finally children. It will be critical to consider the appropriate outcome measures and settings in which to study medication response in adults. The heterogeneity in settings for adults with ASD is a significant impediment to assessing symptom response. Ideally, medications would be combined with an educational or psychosocial intervention that would mirror the school and therapeutic settings in which children with ASD show improvements in social, communication, or behavioral function. Without some level of educational or social challenge, it may be quite difficult to assess medication response.

Research is needed on which outcomes to use in future studies. The Aberrant Behavior Checklist is the best outcome measure for behavioral symptoms in ASD in terms of both validity and reliability, but it does not directly index anxiety, mood, social, or communication function, nor does it capture broader outcomes such as quality of life. More outcome measures are needed to allow assessment of a broader range of symptoms, particularly in individuals who may be higher functioning. No studies provide adequate information on longer-term outcomes, and particularly on outcomes related to achieving goals for independence. To some degree, this reflects a lack of understanding and consensus about optimal outcomes and how to measure them.

Research is also necessary to understand how individuals' expression of ASD symptoms and the severity of symptoms may affect treatment over the lifespan. Foundational research is necessary to understand the goals of individuals with autism and their families as future research studies are planned. Similarly, little research addressing the effects of family and caregiver interactions and characteristics on the responses of individuals' with ASD to interventions exists.

Conclusions

Given the number of individuals affected by ASD, there is a dramatic lack of evidence on best approaches to therapies for adolescents and young adults with these conditions. In particular, families have little in the way of evidence-based approaches to support interventions capable of optimizing the transition of teens with autism into adulthood. Most of the studies identified were of poor quality; while the fair quality studies were primarily of medical interventions. Behavioral, educational, and adaptive/life skills studies were typically small and short term and suggested some improvements in social skills and functional behavior.

Individual studies also suggested that vocational programs may increase employment success, but the studies were small. By the same token, little evidence supports the use of medical or allied health interventions in the adolescent and young adult population. Although the studies that have been conducted focused on the use of medications to address specific challenging behaviors, the effectiveness in managing irritability and aggression in this age group remains largely unknown and can at best be inferred from studies of young children.

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Acronyms and Abbreviations

ABC	Aberrant Behavior Checklist
ABC-C	Aberrant Behavior Checklist-Community Rating Scale
ABC-I	Aberrant Behavior Checklist-Community Rating Scale-Irritability
AHRQ	Agency for Healthcare Research and Quality
ASD	Autism spectrum disorders
BPVS	British Picture Vocabulary Scale
CARS	Childhood Autism Rating Scale
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
FC	Facilitated communication
G	Group
IQ	Intelligence quotient
KBIT2	Kaufman Brief Intelligence Test-Second Edition
KQ	Key question
mg	Milligram
N, n	Number
NA	Not applicable
NR	Not reported
nRCT	Nonrandomized controlled trial
PDA	Personal digital assistant
PDD-NOS	Pervasive Developmental Disorder-Not Otherwise Specified
PEP	PsychoEducational Profile
RCT	Randomized controlled trial
SD	Standard deviation
SIB-Q	Self-Injurious Behavior Questionnaire
SRI	Serotonin reuptake inhibitor
TEACCH	Treatment and Education of Autistic and Communication related Handicapped Children
TEP	Technical Expert Panel
TOO	Task Order Officer
UK	United Kingdom
US	United States
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
Y-BOCS	Yale Brown Obsessive Compulsive Scale