

American Academy of Child and Adolescent Psychiatry

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PRACTICE PARAMETER FOR THE ASSESSMENT AND TREATMENT OF CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

ABSTRACT

Autism spectrum disorder (ASD) is characterized by patterns of delay and deviance in the development of social, communicative, and cognitive skills which arise in the first years of life. Although frequently associated with intellectual disability, this condition is distinctive in terms of its course, impact, and treatment. ASD has a wide range of syndrome expression and its management presents particular challenges for clinicians. Individuals with an ASD can present for clinical care at any point in development. The multiple developmental and behavioral problems associated with this condition necessitate multidisciplinary care, coordination of services, and advocacy for individuals and their families. Early, sustained intervention and the use of multiple treatment modalities are indicated. **Key Words:** autism, practice parameters, guidelines, developmental disorders, pervasive developmental disorders.

ATTRIBUTION

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primary author(s), the CQI, topic experts, and representatives from multiple constituent groups, including the AACAP membership, relevant AACAP Committees, the AACAP Assembly of Regional Organizations, and the AACAP Council. Details of the parameter development process can be accessed on the AACAP Web site. Responsibility for parameter content and review rests with the author(s), the CQI, the CQI Consensus Group, and the AACAP Council.

The AACAP develops both patient-oriented and clinician-oriented Practice Parameters. Patient-oriented parameters provide recommendations to guide clinicians toward best assessment and treatment practices. Recommendations are based on the critical appraisal of empirical evidence (when available) and clinical consensus (when not), and are graded according to the strength of the empirical and clinical support. Clinician-oriented parameters provide clinicians with the information (stated as principles) needed to develop practice-based skills. Although empirical evidence may be available to support certain principles, principles are primarily based on clinical consensus. This parameter is a patient-oriented parameter.

The primary intended audience for the AACAP Practice Parameters is child and adolescent psychiatrists; however, the information contained therein may also be useful for other mental health clinicians.

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INTRODUCTION

Since the first *Practice Parameter for the Assessment and Treatment of Children, Adolescents, and Adults with Autism and Other Pervasive Developmental Disorders*¹ was published, several thousand research and clinical papers have appeared and the diagnostic criteria for autism have changed. This parameter revision provides the opportunity to update the previous version and incorporate new research. As the extant body of research was performed under the DSM-IV TR diagnostic schema, the evidence will be presented utilizing that terminology. This parameter is applicable to evaluation of children and adolescents (age 17 and younger), but often will have some relevance to adults as well. This document presumes basic familiarity with aspects of normal child development and child psychiatric diagnosis and treatment. Unless otherwise noted, the term “child” refers both to adolescents and younger children, and “parents” refers to the child’s primary caretakers regardless of whether they are the biological or adoptive parents or legal guardians.

METHODOLOGY

The first version of this parameter was published in 1999. For this revision, the literature search covered the period 1991 to March 19, 2013 using the PubMed, PsycINFO, Cochrane and CINAHL (EBSCO) databases. The initial searches were inclusive and sensitive. Search terms were a combination of MeSH headings and keywords, and the MeSH headings were adjusted to terms used by PsycINFO and CINAHL by utilizing their thesauri.

In PubMed the MeSH terms Autistic Disorder, Childhood Development Disorders - Pervasive, Asperger*, and Rett*, as well as keyword “autism” were searched. The initial search yielded 20,807 results. Results were then limited to English, human, “all child (0 to 18 years)”

and 1991 to March 19, 2013. Additional limits included: classical article, clinical trial, comparative study, controlled clinical trial, evaluation studies, guideline, historical article, meta-analysis, practice guideline, multicenter study, randomized controlled trial, review, twin study and validation studies. The refined PubMed search yielded 3,613 articles.

In the PsycINFO database subject headings (focused) of autism, autistic thinking, pervasive developmental disorders, retts syndrome, aspergers, and keyword “autism” were searched. The initial search returned 24,875 articles and was then limited to English, “childhood: birth to age 12yrs,” “adolescence: age 13-17 yrs,” “peer reviewed journal,” and 1991 to March 19, 2013. The refined PsycINFO search yielded 9,583 articles.

In the Cochrane Database of Systematic Reviews keywords of autism, autistic, rett*, asperger* or (pervasive and disorder* and develop*) were searched without additional limits. The Cochrane search yielded 95 articles. An additional 517 articles were retrieved from the CINAHL database, after excluding Medline articles, by searching “autistic disorder”, “autism”, “asperger syndrome”, “child development disorders, pervasive” and “rett syndrome”.

A total of 13,808 articles were identified and exported to the EndNote reference management program. After removing duplicate references the resulting yield from the comprehensive search was 9,581 articles.

The titles and abstracts of all articles were reviewed. Studies were selected for full text review based upon their place in the hierarchy of evidence (e.g. randomized controlled trials), quality of individual studies, and generalizability to clinical practice. The search was augmented by review of articles nominated by expert reviewers and further search of article reference lists and relevant textbook chapters. A total of 186 articles were selected for full text examination.

CLINICAL PRESENTATION AND COURSE

Autism was first described in 1943 by Leo Kanner² who reported 11 children with an apparently congenital inability to relate to other people, but who were quite sensitive to change in the nonsocial environment. Kanner emphasized that the lack of interest in people was in stark contrast to the profound social interest of normal infants. He also observed that when language developed at all it was marked by echolalia, pronoun reversal, and concreteness. The children also exhibited unusual, repetitive, and apparently purposeless activities (stereotypies). Autism

was initially believed to be a form of childhood psychosis but, by the 1970s, various lines of evidence made it clear that autism was highly distinctive. By 1980, autism was officially recognized as a diagnosis in DSM-III.³

Under DSM-IV TR, the diagnosis of autism required disturbances in each of three domains: (i) social relatedness, (ii) communication/play, and (iii) restricted interests and activities with onset by age three years.⁴ The disturbance in social relatedness is striking and includes marked impairment in non-verbal communication, peer relationships and social-emotional reciprocity. Impairments in communication include either a delay or total lack of spoken language (without an attempt to compensate through other means) or, for verbal individuals, a marked difficulty in the ability to sustain or initiate conversation, stereotyped and repetitive (or idiosyncratic) language and lack of developmentally-appropriate make-believe or social play. Impairment in interests and activities includes encompassing preoccupations, adherence to apparently non-functional routines or rituals, stereotypies and motor mannerisms, and persistent preoccupation with parts of objects.

There is variability in the age at which children may present the features essential for this diagnosis.⁵ Preschool children with autism typically present with marked lack of interest in others, failures in empathy, absent or severely delayed speech and communication, marked resistance to change, restricted interests, and stereotyped movements. Common parental concerns include a child's lack of language, inconsistencies in responsiveness, or concern that the child might be deaf. In children with autism, social and communication skills usually increase by school age, however, problems dealing with change and transitions and various self-stimulatory behaviors (sometimes including self-injury) may also become more prominent during this time.⁶ In adolescence, a small number of individuals with autism make marked developmental gains; another subgroup will behaviorally deteriorate (e.g. tantrums, self injury or aggression). Children and adolescents with autism have an increased risk for accidental death (e.g., drowning).⁷ Predictors of ultimate outcome include the presence of communicative speech by age 5 and overall cognitive ability (IQ). Evidence that earlier detection and provision of services improves long term prognosis makes early diagnosis particularly important.⁸

The DSM-IV TR category of pervasive developmental disorders included autistic disorder, Rett's disorder, Asperger's disorder, childhood disintegrative disorder and PDD-NOS.

Rett's disorder was described by Andreas Rett in 1966 in a series of girls with unusual hand washing/wringing stereotyped mannerisms. In the majority of cases, Rett's disorder is caused by mutations in the gene MeCP2 (methyl-CpG-binding protein 2).⁹ Head circumference and development are normal at birth and during infancy. Before age 4 years, head growth decelerates, purposeful hand movements are lost, and characteristic stereotyped hand movements (wringing or washing) develop.¹⁰ The central role of MeCP2 mutations in this disorder makes it clear that boys may carry the same mutations that lead to the full syndrome in girls, but with differing clinical manifestations ranging from fatal encephalopathy,¹¹ to progressive but non-fatal developmental disorder,¹² to non-specific X-linked intellectual disability.¹³

Childhood disintegrative disorder was first described by Heller in 1908.¹⁴ This condition is characterized by a period of at least two years of normal development, followed by a marked deterioration and clinically significant loss of at least two skills in the areas of receptive or expressive language, social skills, toileting skills, play, or motor skills.¹⁴ The onset of CDD is highly distinctive, typically occurring between 3 and 4 years of age and can be gradual or abrupt. Sometimes parents report that the child experienced a period of anxiety or dysphoria prior to onset of CDD symptoms. Once established, CDD resembles autism in terms of clinical features,¹⁴ but the outcome is poor. The child typically becomes mute or, at best, regains limited speech.

Asperger's disorder (AspD) was described in 1944 but not officially recognized until DSM-IV. Unlike children with autism, individuals with AspD do not present with delays in language acquisition or with unusual behaviors and environmental responsiveness during the first years of life. Consequently parents often have no concerns about their child's early development.¹⁵ Asperger originally described children who were precocious in learning to talk, but who then talked in a formal, pedantic, one-sided way, often about a topic of circumscribed interest.¹⁶ Social difficulties arise due to this idiosyncratic, one-sided social style. The outcome in Asperger's disorder generally appears to be better than that for autism, although this may, in part, relate to better cognitive and/or verbal abilities.^{8,15}

The term pervasive developmental disorder-not otherwise specified (PDD NOS) (also sometimes termed atypical PDD or atypical autism) encompasses subthreshold cases on the autism spectrum, e.g., cases in which full criteria for one of the explicitly defined PDD's are not

met, but the child has problems in social interaction and some difficulties in communication or restricted patterns of behavior. Although studies are limited, individuals with PDD NOS have typically been characterized as less impaired, having fewer repetitive behaviors, and having a better prognosis than persons with autism.¹⁶

DSM-IV TR to DSM-5

As there was little evidence to support reliable and replicable diagnostic differences amongst the various DSM-IV TR pervasive developmental disorders,¹⁷ the DSM-5 workgroup on neurodevelopmental disorders subsumed the prior categories under the new diagnosis of autism spectrum disorder in the DSM-5. Diagnostic domains were reduced from three to two, focusing upon social communication deficits and restricted, repetitive behaviors. The strict requirement for onset prior to three years of age was changed to onset in the early developmental period, the occurrence of potential sensory abnormalities was incorporated, and a symptom severity level scale (see Table 1) was included. It will be a number of years before the implications of these changes for autism prevalence and other facets of assessment and treatment can be fully assessed. A comparison of the DSM-5 and the DSM IV-TR criteria appears in Table 2.

EPIDEMIOLOGY

A number of studies, mostly conducted outside the U.S., have examined the prevalence of autism, or less commonly, autism spectrum disorder (ASD) or pervasive developmental disorders (PDDs).¹⁷ Of the approximately 36 surveys of autism available, prevalence estimates for autistic disorder range from 0.7/10,000 to 72.6/10,000.¹⁸ The variability in estimates reflects a number of factors including changes in definition. When the 18 surveys conducted since the introduction of the DSM-IV criteria are considered, estimates ranging from 10/10,000 to 16/10,000, with a median prevalence of 13/10,000, are obtained.¹⁸ The most recent study by the Centers for Disease Control estimated the prevalence of ASD in the United States as 11.3/1000.¹⁹ Contrary to popular perception, data from seven surveys suggest that rates of Asperger's disorder are in fact *lower* than typical autism (2.6/10,000 or one-fifth as common as typical autism).¹⁸

Recent observations of higher rates of autism have led to concern that the prevalence of this disorder may be increasing. Various factors may contribute to an apparent increase,²⁰ such as

differences in diagnostic criteria and diagnostic practices, the age of children screened, and the location of the study (see Fombonne¹⁸ for discussion).

Autism is approximately four times more common in males than in females, but females with autism tend to have more severe intellectual disability. Although Kanner's original report² suggested a predominance of autism in more educated families, subsequent work has not shown this. Current approaches to the diagnosis of ASD appear to work well internationally and cross-culturally,³ although cultural aspects of the condition have not received much attention.²¹ Within the U.S. there may be under diagnosis in some circumstances, e.g. among disadvantaged inner-city children.²²

ETIOLOGY

Neurobiology

Electroencephalographic (EEG) abnormalities and seizure disorders are observed in as many as 20 to 25% of individuals with autism.²³ The high rates of epilepsy suggest a role for neurobiologic factors in autism.^{13,24,25} The number of areas affected by autism suggests that a diverse and widely distributed set of neural systems must be affected. Although various theories have posited potential loci for difficulties, definitive data are lacking. Postmortem studies have revealed various abnormalities, particularly within the limbic system.²⁵ Functional MRI procedures have identified difficulties in tasks involving social and affective judgments and differences in the processing of face and nonface stimuli.²⁶ Structural MRI has revealed an overall brain size increase in autism, and diffusion tensor imaging studies have suggested aberrations in white matter tract development.²⁷ One of the most frequently replicated neurochemical findings has been the elevation of peripheral levels of the neurotransmitter serotonin. The significance of this finding remains unclear. A role for dopamine is suggested given the problems with over activity and stereotyped mannerisms and the positive response of such behaviors to neuroleptic medications.²⁸

During the last decade, much concern has focused on vaccines as a possible post-natal environmental cause for ASD with the concern focused either on the possibility that the MMR vaccine may cause autism or that thimerosal (a mercury containing preservative now removed from all single dose vaccines) might do so.²⁹ The preponderance of available data has not

supported either hypothesis (see Rutter³⁰ for a review). However, a possible role of the immune system in some cases of autism has not been ruled out.³¹

Neuropsychological correlates of ASD include impairments in executive functioning (e.g., simultaneously engaging in multiple tasks),³² weak central coherence (integrating information into meaningful wholes),³³ and deficits in theory of mind tasks (taking the perspective of another person).³⁴

Familial Pattern and Genetic Factors

The high recurrence risk for autism among siblings and even higher concordance for autism in identical twins has provided strong support for the importance of genetic factors.³⁰ Higher rates of autism are consistently noted in siblings of affected children. Recurrence risk has typically been cited at 2-10%, but a recent prospective longitudinal study reported a rate of 18.7% when the broad autism spectrum is considered.³⁵ Identified risk factors for ASD appear to include closer spacing of pregnancies, advanced maternal or paternal age, and extremely premature birth (<26 weeks gestational age).³⁶⁻³⁸ In addition, high rates of learning/language problems and social disability, as well as a possible increase in the risk for mood and anxiety disorders has been noted in family members as well.

It is now clear that multiple genes are involved in autism.^{30,39} Over the past several years, studies have supported a role for both common (present in more than 5 percent of the general population) and rare genetic variation contributing to autism.⁴⁰ The rate of progress in gene discovery has been increasing rapidly over the last several years and these results are already beginning to influence clinical practice with regard to genetic testing as noted below.⁴¹

DIFFERENTIAL DIAGNOSIS

ASD must be differentiated from specific developmental disorders (including language disorders), sensory impairments (especially deafness), reactive attachment disorder, obsessive compulsive disorder, intellectual disability, anxiety disorders including selective mutism, childhood onset schizophrenia, and other organic conditions.

A diagnosis of autism is made when the requisite DSM-5 symptoms are present and other disorders have been adequately ruled out. In autism it is typical for parents to report that there

was no period of normal development or that there was a history of unusual behaviors (e.g., the child seemed too good and undemanding as an infant). Less commonly, a period of apparently normal development is reported before a regression (loss of skills). The topic of regression in autism remains an active area of current investigation. Developmental regression is typical in Rett's, but can also be observed in other conditions (e.g., childhood onset schizophrenia or degenerative CNS disorders).

Developmental language disorders have an impact on socialization and may be mistaken for an ASD. The distinction is particularly difficult in preschool children. However, two behaviors have been reported to consistently differentiate autistic children from language impaired peers at both 20 and 42 months; namely, pointing for interest and use of conventional gestures.⁴² Similarly, differentiating between mild to moderate developmental delay and ASD may be difficult, particularly when evaluating the younger child (see Chawarska et al.⁴² for a detailed discussion). One study identified a number of items on the Autism Diagnostic Interview (ADI-R) (see Table 3) that differentiated between these two groups at 24 months, especially directing attention (showing) and attention to voice. At 36 months, four items correctly classified all subjects: use of other's body, attention to voice, pointing, and finger mannerisms. Between 38 and 61 months, children with autism were more likely to show impaired nonverbal behaviors (such as eye contact) to regulate social interaction. In childhood, there may be diagnostic overlap between ASD and attention-deficit/hyperactivity disorder (ADHD), making the differential diagnosis difficult.^{43,44}

Children with reactive attachment disorder may exhibit deficits in attachment and therefore inappropriate social responsivity, but these usually improve substantially if adequate caretaking is provided. Obsessive-compulsive disorder has a later onset than ASD, is not typically associated with social and communicative impairments, and is characterized by repetitive patterns of behavior that are ego dystonic. Symptoms that characterize anxiety disorders, such as excessive worry, the need for reassurance, the inability to relax, and feelings of self-consciousness are also seen in ASD, particularly among higher functioning individuals. However, the two conditions can be differentiated by the prominent social and communicative impairments seen in ASD but not anxiety disorders, and the developed social insight of children with anxiety disorders, which is not seen in ASD. Differentiating childhood schizophrenia from

autism can be difficult, as both are characterized by social impairments and odd patterns of thinking. However, florid delusions and hallucinations are rarely seen in autism.

COMORBIDITIES

Given difficulties in communication (e.g., mutism) and cognitive impairment, issues of comorbidity in ASD can be quite complex. The process of diagnostic overshadowing (the tendency to fail to diagnosis other comorbid conditions when a more noticeable condition is present) may occur.⁴⁵ Attempts to determine comorbidity prevalence in ASD have been hampered by methodological issues, though most studies show increased rates of anxiety and attentional disorders.⁴⁶

In most epidemiologically-based samples of persons with autistic disorder, approximately 50% exhibit severe or profound intellectual disability (ID), 35% exhibit mild to moderate ID, and the remaining 20% have IQs in the normal range.¹⁸ For children with autistic disorder, verbal skills are typically more impaired than nonverbal skills. For children with Asperger's, the reverse pattern is sometimes observed and the profile of nonverbal learning disability may be present.⁴⁷ Clearly, intellectual impairment is not an essential diagnostic feature of autism, and it is thus necessary and important for the diagnosis of ID to be made.

A range of behavioral difficulties can be observed in ASD including hyperactivity, obsessive-compulsive phenomena, self-injury, aggression, stereotypies, tics, and affective symptoms. The issue of whether these qualify as additional disorders is complex.³ Affective symptoms are frequently observed and include lability, inappropriate affective responses, anxiety, and depression. Impairments in emotion regulation processes can lead to under and over reactivity.⁴⁸ Overt clinical depression is sometimes observed and this may be particularly true for adolescents with Asperger's disorder.¹⁵ Case reports and case series suggest possible associations with bipolar disorders and tics and Tourette's syndrome. Bullying involvement, including victimization and perpetration, occurs more frequently in general educational settings.⁴⁹

Attentional difficulties are also frequent in autism, reflecting cognitive, language, and social problems.⁵⁰ The historical prohibition on making an additional diagnosis of ADHD in those with ASD has been removed in the DSM-5. Notably, a subset of children with ASD with

elevated scores for hyperactivity showed a 49% response rate in a large RCT of methylphenidate treatment.⁵⁰

EVIDENCE BASE FOR PRACTICE PARAMETERS

In this parameter, recommendations for best assessment and treatment practices are stated in accordance with the strength of the underlying empirical and/or clinical support, as follows:

- Clinical Standard [CS] is applied to recommendations that are based on rigorous empirical evidence (e.g., meta-analyses, systematic reviews, individual randomized controlled trials) and/or overwhelming clinical consensus
 - Clinical Guideline [CG] is applied to recommendations that are based on strong empirical evidence (e.g., non-randomized controlled trials, cohort studies, case-control studies) and/or strong clinical consensus
 - Clinical Option [OP] is applied to recommendations that are based on emerging empirical evidence (e.g., uncontrolled trials or case series/reports) or clinical opinion, but lack strong empirical evidence and/or strong clinical consensus
- Not Endorsed [NE] is applied to practices that are known to be ineffective or contraindicated

The strength of the empirical evidence is rated in descending order as follows:

- [rct] Randomized, controlled trial is applied to studies in which subjects are randomly assigned to two or more treatment conditions
- [ct] Controlled trial is applied to studies in which subjects are non-randomly assigned to two or more treatment conditions
- [ut] Uncontrolled trial is applied to studies in which subjects are assigned to one treatment condition
- [cs] Case series/report is applied to a case series or a case report

ASSESSMENT

Recommendation 1. *The developmental assessment of young children and the psychiatric assessment of all children should routinely include questions about autism spectrum disorder symptomatology [CS].*

Screening should include inquiries about the core symptoms of ASD, including social relatedness and repetitive or unusual behaviors. Screening instruments have been developed (see Table 3) that may be helpful to the clinician. Some of these instruments are completed by clinicians and others by primary caregivers. Screening is applicable both to young children and to infants, where the diagnosis may first be considered. In some instances screening may be relevant to older children, e.g., those who are more intellectually able and whose social disability is therefore more likely to be detected later.

Recommendation 2. *If the screening indicates significant autism spectrum disorder symptomatology, a thorough diagnostic evaluation should be performed to determine the presence of ASD [CS].*

At present, biological diagnostic markers are not available and diagnosis rests on careful examination of the child. A standard psychiatric assessment should be followed,⁵¹ including interviews with the child and family, and a review of past records and historical information. The history and examination should be conducted with careful consideration of DSM-5 diagnostic criteria. Although the DSM-5 criteria are intended to be age and intellect independent, the diagnosis of autism in infants and very young children is more challenging, and some features (e.g., stereotyped movements) may develop later.⁵ Systematic attention to the areas relevant to differential diagnosis is essential. Information on the nature of changes over the course of development, e.g., in response to intervention, is helpful. The history should include a review of past and current educational and behavioral interventions, as well as information regarding family history and relevant psychosocial issues. Consideration of possible comorbid diagnoses is an important focus of assessment.

Observation of the child should focus on broad areas of social interaction and restricted, repetitive behaviors. The child's age and developmental level may dictate some modification in assessment procedures. Clinicians should be sensitive to ethnic, cultural or socio-economic factors which may impact assessment.

Various instruments for the assessment of ASD have been developed (Table 3, see Coonrod and Stone⁵² for a review). As a practical matter, all of these instruments vary in their usefulness for usual clinical practice. Some require specific training. The use of such instruments supplements, but does not replace, informed clinical judgment.³

Recommendation 3. *Clinicians should coordinate an appropriate multi-disciplinary assessment of children with ASD [CS].*

All children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of Tuberous Sclerosis, and genetic testing, which may include G-banded karyotype, Fragile X testing or chromosomal microarray (CMA). In a community sample of children with ASD, diagnostic yield was 2.5% for karyotype testing, 0.57% for Fragile X testing and 24% for CMA.⁵³ CMA has been recommended by medical geneticists as the standard of care for the initial evaluation of children with developmental disabilities and/or autism spectrum disorders.⁵⁴ These tests currently detect both known abnormalities clearly associated with increased rates of ASD (e.g. 15q11-13 maternal duplications and duplications and deletions of chromosome 16p11.2) as well as genetic variations of uncertain significance. Recent data from the study of families with only a single affected child have demonstrated that lower IQ is not a strong predictor of a positive chromosomal finding.⁵⁵ Any abnormal or indeterminate result from such a study warrants referral for further genetic evaluation and counseling. The yield of genetic testing in the presence of clinical suspicion is currently in the range of 1/3 or more of cases.⁵⁶

Unusual features in the child (e.g., history of regression, dysmorphism, staring spells, family history) should prompt additional evaluations. The list of potential organic etiologies is large, but falls into the categories of infectious (e.g., encephalitis or meningitis), endocrinological (e.g., hypothyroidism), metabolic (e.g., homocystinuria), traumatic (e.g., head injury), toxic (e.g., fetal alcohol syndrome),⁴ or genetic (e.g., chromosomal abnormality). Certain developmental disorders, most notably Landau-Kleffner syndrome, also should be ruled out. In this condition, a highly distinctive EEG abnormality is present and associated with development of a marked aphasia.⁵⁷ Genetic or neurological consultation, neuroimaging, EEG, and additional laboratory

tests should be obtained when relevant, based on examination or history (e.g., testing for the MeCP2 gene in cases of possible Rett's Disorder).⁵⁸

Psychological assessment, including measures of cognitive ability and adaptive skills, is indicated for treatment planning and helps to frame observed social-communication difficulties relative to overall development. The results of standard tests of intelligence may reveal considerable scatter. Unusual islets of ability ("splinter skills") may be present. For children with autism, these sometimes take the form of unusual ability ("savant skills"), for example, the ability to produce intricate drawings or engage in calendar calculations. For higher functioning children, areas of special interest are often present and the single-minded pursuit of these interests may interfere with the child's ability to learn. Psychological tests clarify areas of strength and weakness useful in designing intervention programs and may need to include instruments valid for a non-verbal population.⁷

Communication assessment, including measures of both receptive and expressive vocabulary as well as language use (particularly social or pragmatic), is helpful relative to diagnosis and treatment planning.⁵⁹ Occupational and physical therapy evaluations may be needed to evaluate sensory and/or motor difficulties.⁶⁰ Sleep is also an important variable to assess in individuals with ASD.⁶¹ When members of multiple disciplines are involved in assessment it is optimal that coordination occur between the various professionals.

TREATMENT

Recommendation 4. *The clinician should help the family obtain appropriate, evidence-based and structured educational and behavioral interventions for children with ASD [CS].*

Structured educational and behavioral interventions have been shown to be effective for many children with ASD⁶² and are associated with better outcome.⁸ As summarized in the National Research Council (NRC)⁶² report, the quality of the research literature in this area is variable, with most studies employing group controls or single-subject experimental methods. In general, studies employing more rigorous randomized group comparisons are sparse, reflecting difficulties in random assignment and control comparisons. Other problems include lack of attention to subject characterization, generalization of treatment effects, and fidelity of treatment implementation. Despite these problems, various comprehensive treatments approaches have

been shown to have efficacy for groups of children, although none of the comprehensive treatment models has clearly emerged as superior.⁶²

Behavioral

Behavioral interventions such as Applied Behavioral Analysis (ABA) are informed by basic and empirically supported learning principles.⁶³ A widely disseminated comprehensive ABA program is Early Intensive Behavioral Intervention (EIBI) for young children, based on the work of Lovaas et al.⁶⁴ EIBI is intensive and highly individualized with up to 40 hours per week of one to one direct teaching, initially using discrete trials to teach simple skills and progressing to more complex skills such as initiating verbal behavior. A meta-analysis found EIBI effective for young children, but stressed the need for more rigorous research to extend the findings.⁶⁵ Behavioral techniques are particularly useful when maladaptive behaviors interfere with provision of a comprehensive intervention program. In such situations a functional analysis of the target behavior is performed, in which patterns of reinforcement are identified and then various behavioral techniques are used to promote a desired behavioral alternative. ABA techniques have been repeatedly shown to have efficacy for specific problem behaviors,⁶⁶ and ABA has also been found to be effective as applied to academic tasks,^{67[ut]} adaptive living skills,^{68[ut]} communication,^{69[ut]} social skills,^{70[ut]} and vocational skills.^{71[ct]} Because most children with ASD tend to learn tasks in isolation, an explicit focus on generalization is important.⁷²

Communication

Communication is a major focus of intervention and typically will be addressed in the child's Individualized Educational Plan (IEP) in coordination with the speech-language pathologist. Children who do not yet use words can be helped through use of alternative communication modalities such as sign language, communication boards, visual supports, picture exchange, and other forms of augmentative communication. There is some evidence for the efficacy of the Picture Exchange Communication System (PECS), sign language, activity schedules and voice output communication aids.^{73[rct],74,75,76} For individuals with fluent speech the focus should be on pragmatic language skills training. Children and adolescents with fluent speech may, for example, be highly verbal but have severely impaired pragmatic language skills that can be addressed through explicit teaching. A range of programs to enhance social

reciprocity and pragmatic language skills are now available (see Table 4 and Reichow, 2010 for an extensive review⁷⁷).

Educational

There is a consensus that children with ASD need a structured educational approach with explicit teaching.⁶² Programs shown to be effective typically involve planned, intensive, individualized intervention with an experienced, interdisciplinary team of providers, and family involvement to ensure generalization of skills. The educational plan should reflect an accurate assessment of the child's strengths and vulnerabilities with an explicit description of services to be provided, goals and objectives, and procedures for monitoring effectiveness. Although curricula employed vary across programs they often share goals of enhancing verbal and nonverbal communication, academic skills, and social, motor and behavioral capabilities. In some instances, particularly for younger children, a parent-education and home component may be important. Development of an appropriate IEP is central in providing effective service to the child and family. Efficacy has been shown for two of the structured educational models, the Early Start Denver Model (ESDM)^{78[rct]} and the Treatment and Education of Autism and related Communication handicapped Children program (TEACCH),^{79[ct]} but significant challenges remain in disseminating knowledge about effective interventions to educators.

Other Interventions

There is a lack of evidence for most other forms of psychosocial intervention, though cognitive behavioral therapy (CBT) has shown efficacy for anxiety and anger management in high functioning youth with ASD.^{80[rct],81[rct]} Studies of sensory oriented interventions, such as auditory integration training (AIT), sensory integration therapy (SIT) and touch therapy/massage, have contained methodological flaws and have yet to show replicable improvements.^{82,83} There is also limited evidence thus far for what are usually termed developmental, social-pragmatic models of intervention, such as Developmental-Individual Difference-Relationship Based (DIR)/Floortime, Relationship Development Intervention (RDI), Social Communication Emotional Regulation and Transactional Support (SCERTS) and Play and Language for Autistic Youths (PLAY), which generally use naturalistic techniques in the child's community setting to develop social communication abilities. Finally, children with ASD are psychiatrically hospitalized at substantially higher rates than the non-ASD child population.⁸⁴ The efficacy of

this intervention is unknown, though there is preliminary evidence for the efficacy of hospital psychiatry units that specialize in the population.⁸⁵

Recommendation 5. *Pharmacotherapy may be offered to children with ASD where there is a specific target symptom or comorbid condition [CG].*

Pharmacological interventions may increase the ability of persons with ASD to profit from educational and other interventions, and to remain in less restrictive environments through the management of severe and challenging behaviors. Frequent targets for pharmacological intervention include associated comorbid conditions (e.g., anxiety, depression) and other features such as aggression, self-injurious behavior, hyperactivity, inattention, compulsive-like behaviors, repetitive or stereotypic behaviors, and sleep disturbances. As with other children and adolescents, various considerations should inform pharmacological treatment.⁸⁶ Risperidone^{87[rect]} and aripiprazole^{88[rect]} have been approved by the FDA for the treatment of irritability, consisting primarily of physical aggression and severe tantrum behavior, associated with autism. There is a growing body of controlled evidence for pharmacologic intervention,⁸⁹ and a summary of randomized controlled trials (RCTs) of medication in children with ASD is included (Table 5). Combining medication with parent training is moderately more efficacious than medication alone for reducing serious behavioral disturbance, and modestly more efficacious for adaptive functioning.^{90[rect],91[rect]} Individuals with ASD may be nonverbal, so treatment response is often judged by caregiver report and observation of specific behaviors. While this may help document the effectiveness of the selected medication, one must remember that an overall goal of treatment is to facilitate the child's adjustment and engagement with educational intervention. Several objective rating scales are also available to help monitor treatment response.⁹²

Recommendation 6. *The clinician should maintain an active role in long term treatment planning and family support as well as support of the individual [CG].*

Children and families' need for help and support will vary over time. The clinician should develop a long-term collaboration with the family and realize that service utilization may be sporadic. For very young children, issues of diagnosis and identification of treatment programs will often be most important. For school age children, psychopharmacological and behavioral

issues typically become more prominent. For adolescents, vocational and prevocational training and thoughtful planning for independence/self-sufficiency is important. As part of this long-term engagement, parents and siblings of children with ASD will need support (Table 6). Though raising a child with autism presents major challenges, rates of parental separation and divorce are not higher among parents of children with ASD than those with non-ASD children.⁹³

Recommendation 7. Clinicians should specifically inquire about the use of alternative/complementary treatments, and be prepared to discuss their risk and potential benefits [CS].

Although most alternative or complementary treatment approaches have very limited empirical support for their use in children with ASD they are commonly pursued by families.⁹⁴ It is important that the clinician be able to discuss these treatments with parents, recognizing the motivation for parents to seek all possible treatments. In most instances, these treatments have little or no proven benefit, but also have little risk.⁷ In a few instances, the treatment has been repeatedly shown not to work (e.g., IV infusion of secretin⁹⁵ and oral vitamin B6-magnesium^{96[rct]}), or randomized controlled evidence does not support its use (e.g. the gluten-free, casein-free (GF/CF) diet,⁹⁷ omega-3 fatty acids⁹⁸ and oral human immunoglobulin).^{99[rct]} Some treatments have greater potential risk to the child either directly (e.g., mortality and morbidity associated with chelation^{100[cs]} or via side effects due to contaminants in “natural” compounds, or indirectly (e.g., by diverting financial or psychosocial resources) (for a detailed review of alternative treatments see Jacobson et al.¹⁰¹ and Levy & Hyman¹⁰²). While more controlled studies of these treatments are needed, it is important that the family be able to voice their questions to health care providers. Families may be guided to the growing body of work on evidence based treatments in autism.¹⁰³

PARAMETER LIMITATIONS

AACAP Practice Parameters are developed to assist clinicians in psychiatric decision making. These parameters are not intended to define the sole standard of care. As such, the parameters should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care directed at obtaining the desired results. The ultimate judgment regarding the

care of a particular patient must be made by the clinician in light of all of the circumstances presented by the patient and his or her family, the diagnostic and treatment options available, and available resources.

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Table 1: ASD Symptom Severity Levels

Severity Level	Social Communication	Restricted, Repetitive Behaviors
<p>Level 3 – “Requiring very substantial support”</p>	<p>Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning; very limited initiation of social interactions and minimal response to social overtures from others. e.g. someone with few words of intelligible speech, rarely initiates interaction, and when does so makes unusual approaches to meet needs only, responds to only very direct social approaches.</p>	<p>Inflexibility of behavior, extreme difficulty coping with change, or other restricted/ repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.</p>
<p>Level 2 – “Requiring substantial support”</p>	<p>Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions and reduced or abnormal response to social overtures from others. e.g., a person who speaks simple sentences, interaction limited to narrow special interests, markedly odd nonverbal communication.</p>	<p>Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.</p>
<p>Level 1 – “Requiring support”</p>	<p>Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions, e.g. a person able to speak in full sentences, engages in communication but to-and-fro of conversation fails, attempts to make friends are odd and typically unsuccessful.</p>	<p>Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.</p>

Table 2: Comparison of DSM-5 and DSM-IV TR Diagnostic Criteria for Autism

DSM-5	DSM-IV TR
<p>Autism Spectrum Disorder</p> <p>A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:</p> <ol style="list-style-type: none"> 1. deficits in social-emotional reciprocity. 2. deficits in nonverbal communicative behaviors used for social interaction. 3. deficits in developing, maintaining, and understanding relationships. <p>B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following, currently or by history:</p> <ol style="list-style-type: none"> 1. stereotyped or repetitive motor movements, use of objects, or speech. 2. insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior. 3. highly restricted, fixated interests that are abnormal in intensity or focus. 4. hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment. <p>C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities).</p> <p>D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.</p> <p>E. These disturbances are not better explained by intellectual disability or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.</p>	<p>Autistic Disorder</p> <p>A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):</p> <ol style="list-style-type: none"> (a) qualitative impairment in social interaction, as manifested by at least two of the following: <ol style="list-style-type: none"> (a) marked impairment in the use of multiple nonverbal behaviors (b) failure to develop peer relationships appropriate to developmental level (c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (d) lack of social or emotional reciprocity (2) qualitative impairments in communication as manifested by at least one of the following: <ol style="list-style-type: none"> (a) delay in, or total lack of, the development of spoken language (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others (c) stereotyped and repetitive use of language or idiosyncratic language (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level (3) restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following: <ol style="list-style-type: none"> (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus (b) apparently inflexible adherence to specific, nonfunctional routines or rituals (c) stereotyped and repetitive motor mannerisms (d) persistent preoccupation with parts of objects <p>(d) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.</p>

	(e) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.
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Table 3: Summary of Selected Assessment Instruments for Autism Spectrum Disorder*

Scale (see legend)	Uses	Age Range	Method of Administration	Population Studied	Scale characteristics	Reference
ABC	Screening	Children	Parent rated	AD	57 items, scale 1-4	Krug et al., 1980 ¹⁰⁴
CARS	Screening	Children	Clinician rated	AD	15 items, scale 1-4	Schopler et al., 1980 ¹⁰⁵
M-CHAT	Screening	Toddlers	Parent rated	AD	23 items, 'yes' 'no'	Robins et al., 2001 ¹⁰⁶
CSBS-DP-IT-Checklist	Screening	Toddlers	Parent Rated	AD	24 items	Wetherby et al., 2008 ¹⁰⁷
ASQ	Screening	Child/Adult	Parent rated	AD/AspD	40 items, 'yes' 'no'	Berument et al., 1999 ¹⁰⁸
AQ	Screening	Adults	Self completed	AspD	52 items, scale 0-3	Baron-Cohen et al., 2001 ¹⁰⁹
CAST	Screening	4-11 years	Parent rated	AspD	39 items, 'yes' 'no'	Scott et al., 2002 ¹¹⁰
ADI	Diagnostic	Child/Adult	Interview + clinician rated	AD/AspD	See text	Lord et al., 2003 ¹¹¹
DISCO	Diagnostic	Child/Adult	Interview + clinician rated	AD/AspD	See text	Wing et al., 2002 ¹¹²
ADOS	Diagnostic	Child/Adult	Semi-structured interactive session	AD/AspD	See text	Lord et al., 1994 ¹¹³
ASDS	Diagnostic	5-18 years	Parent rated	AspD	50 items, 'yes' 'no'	Myles et al., 2000 ¹¹⁴
GADS	Diagnostic	3-22 years	Parent + clinician rated	AspD	38 items, scale 0-3	Gilliam, 2001 ¹¹⁵
ASDI	Diagnostic	Child/Adult	Interview + clinician rated	AspD	20 items, 'yes' 'no'	Gillberg et al., 2001 ¹¹⁶
SRS	Diagnostic	4-8 years	Parent or teacher rated	AspD	65 items	Constantino et al., 2003 ¹¹⁷

Abbreviations: ABC=Autism Behaviour Checklist; CARS=Childhood Autism Rating Scale; CHAT=Checklist for Autism in Toddlers; CSBS-DP-IT-Checklist=Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist; ASQ=Autism Screening Questionnaire; AQ=Autism Quotient; CAST=Childhood Autism Screening Test; ADI=Autism Diagnostic Interview – Revised; DISCO=Diagnostic Interview for Social and Communication Disorders; ADOS=Autism Diagnostic Observation Schedule; ASDS=Asperger Syndrome Diagnostic Scale; GADS=Gilliam Asperger Disorder Scale; ASDI=Asperger Syndrome Diagnostic Interview; SRS=Social Responsiveness Scales; Parent = primary caregiver

* Note that these instruments may need to be revised to provide evidence of validity for DSM-5 ASD, and supplement but DO NOT REPLACE clinical diagnosis.

Table 4: Methods Available for the Delivery of Social Reciprocity/Social Pragmatic Oriented Interventions

Developmental Level	Method	Notes	Reference
Infant/ Pre-school (play based)	Guided Participation	Adult coaching & mediation by trained peers	Schuler and Wolfberg, 2002 ¹¹⁸
	Do-Watch-Listen-Say	Careful selection of play materials to foster participation; organisation of the environment to facilitate participation and co-operation.	Quill, 2000 ¹¹⁹
	Play Organizers	Neurotypical peers taught to encourage sharing, helping and praising to facilitate play. Some evidence of generalization.	Strain et al., 1977 ¹²⁰
	Buddy Skills	Teaches neurotypical peers to stay with, play with and talk to their “buddies.” Some evidence of improvement in the frequency of social communication that was generalized to other interactions.	Goldstein and Wikstrom, 1986 ¹²¹
School-aged	Social Stories	State a problem and give the child an acceptable response to it. Usually focuses on maladaptive behaviors. Little evidence of generalization and maintenance.	Gray, 2000 ¹²²
	Social skills groups	(see text)	Kamps et al., 1997 ¹²³
	Peer Network/Circle of Friends	Typical peers taught to initiate and model appropriate social interactions. Results have shown improvement in interaction and generalization to new settings.	Kamps et al., 1997 ¹²³ Whitaker et al., 1998 ¹²⁴
Adolescence	Peer Network/Circle of Friends	(see above)	Whitaker et al., 1998 ¹²⁴ Paul, 2003 ¹²⁵
	Visual schedule/verbal rehearsal	Using written and pictorial representations of expected activities and behaviour	Klin and Volkmar, 2000 ¹²⁶ Hodgdon, 1995 ¹²⁷
	Social skills group	(see text)	Paul, 2003 ¹²⁵
	Social Thinking	Addresses underlying social cognitive knowledge required for expression of related social skills; promotes teaching the “why” behind socialization.	Crooke, 2007 ¹²⁸
	Training scripts	Scripts are provided that give the opportunity to ask questions in response to others= initiation of conversation	Klin, 1997 ¹²⁹

Table 5: Randomized Controlled Trials of Psychotropic Medications in Children and Adolescents with ASD

Agent	Study	Target Symptoms	Dose	Demographics	Significant Side Effects	Primary Outcome(s)
<i>Alpha-2 Agonists</i>						
Clonidine	Jaselskis et al., 1992 ¹³⁰	Hyperactivity, Irritability, Inappropriate speech, Stereotypy	0.15-0.20mg divided TID	8 children 5-13 yo	Hypotension, drowsiness	Statistically and clinically relevant decrease in ABC Irritability subscale.
Guanfacine	Handen, et al., 2008 ¹³¹	Hyperactivity, Inattention	1-3 mg divided TID	7 children with ASD, 5-9 yo	Drowsiness, irritability	45% with a >50% decrease in ABC Hyperactivity subscale
<i>Antipsychotics</i>						
Aripiprazole	** Marcus, et al., 2009 ¹³²	Irritability, Hyperactivity, Stereotypy, Social withdrawal Inappropriate speech	5, 10 or 15 mg per day, fixed dose	218 children 6-17 yo	Somnolence, weight gain, drooling, tremor, fatigue, vomiting	56% positive response* for 5 mg aripiprazole vs. 35% on placebo Significant improvement in Irritability, Hyperactivity and Stereotypy subscales.
	** Owen, et al., 2009 ¹³³	Irritability, Hyperactivity, Stereotypy, Social withdrawal Inappropriate speech	5-15 mg per day, flexibly dosed	98 children 6-17 yo	Somnolence, weight gain, drooling, tremor, fatigue, vomiting	52% positive response* for aripiprazole vs. 14% on placebo. Significant improvement in Irritability, Hyperactivity & Stereotypy subscales.
Haloperidol	Anderson, et al., 1984 ¹³⁴	Multiple behavioral symptoms, Global functioning	0.5-4 mg per day	40 children 2 – 7 yo	Sedation, irritability, extrapyramidal symptoms (>25%)	Behavioral symptoms improved with significant decrease in 8 of 14 items of the CPRS (Children's Psychiatric Rating Scale).
	Anderson, et al., 1989 ¹³⁵	Multiple behavioral symptoms, Global functioning	0.25-4 mg per day	45 children 2-7 yo	Sedation, extrapyramidal symptoms	Behavioral symptoms improved with significant decrease in 7 of 14 items of the CPRS.
Olanzapine	** Hollander, et al., 2006 ¹³⁶	Global functioning, Aggression, Compulsions, Irritability	7.5-12.5 mg per day	11 children 6-14 yo	Weight gain, sedation	50% of those on olanzapine much or very much improved in global functioning vs. 20% on placebo
Risperidone	RUPP, 2002 ¹³⁷	Irritability, Hyperactivity, Stereotypy, Social	0.5-3.5 mg per day	101 children 5-17 yo	Weight gain, increased appetite, fatigue,	69% had a positive response* on risperidone vs. 12% positive

Agent	Study	Target Symptoms	Dose	Demographics	Significant Side Effects	Primary Outcome(s)
		withdrawal, Inappropriate speech			drowsiness, drooling, dizziness	response* on placebo. Significant positive findings for hyperactivity and stereotypy
	** Shea, et al., 2004 ¹³⁸	Irritability, Hyperactivity, Stereotypy, Social withdrawal Inappropriate speech	0.02-0.06 mg/kg/day	79 children 5-12 yo	Weight gain, somnia,	64% improvement in ABC Irritability on risperidone vs. 31% improvement on placebo. Significant positive finding for hyperactivity
	McDougle, et al., 2005 ¹³⁹	Social and communication impairment, Repetitive behavior & Stereotypy	0.5-3.5 mg per day	101 children 5-17 yo	Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness	Significant response*** for repetitive behavior and stereotypy on risperidone
Risperidone vs. Haloperidol	** Miral, et al., 2008 ¹⁴⁰	Behavior, Social, Sensory, Language	0.01-0.08 mg/kg/day	30 children 8-18 yo	EPS, weight gain. gynecomastia	Risperidone reported superior to haloperidol only on ABC Total score, no sub-scales reported.
<i>Mood Stabilizers</i>						
Valproic Acid	Hellings, et al., 2005 ¹⁴¹	Irritability	20 mg/kg/day avg level 75-78	30 subjects 6-20 yo	Increased appetite, skin rash	No significant difference for ABC Irritability sub-scale
	** Hollander, et al., 2005 ¹⁴²	Repetitive Behavior	500-1500 mg per day	12 children 5-17 yo, and 1 adult, 40 yo	Irritability, aggression	Statistically significant decrease in repetitive behavior on C- YBOCS
	Hollander, et al., 2010 ¹⁴³	Global irritability	Dosed to a mean level of 89.8 mcg per ml	27 children 5-17 yo	Skin rash, irritability	62.5% positive response for irritability on the CGI on divalproex vs. 9.09% on placebo.
Lamotrigine	** Belsito, et al., 2001 ¹⁴⁴	Irritability, Social behavior	5 mg per kg per day	28 children 3-11 yo	Insomnia, hyperactivity	No significant difference in irritability or social behavior on multiple instruments.
Levetiracetam	** Wasserman, et al., 2006 ¹⁴⁵	Irritability Global functioning	20-30 mg per kg/day	20 children 5-17 yo	Aggression	No significant difference in global functioning or irritability
<i>Norepinephrine Reuptake Inhibitors</i>						

Agent	Study	Target Symptoms	Dose	Demographics	Significant Side Effects	Primary Outcome(s)
Atomoxetine HCl	**Harfterkamp, M, et al., 2012 ¹⁴⁶	Hyperactivity Inattention	1.2 mg/kg/day	97 children 6-17 yo	Nausea, anorexia Fatigue, early wakening	Significant difference in the ADHD-RS for active treatment group. No difference in CGI-I
	** Arnold, et al., 2006 ¹⁴⁷	Hyperactivity Inattention	20-100mg divided bid mean 44mg/day	16 children 5-15 yo	Upper G.I. symptoms, fatigue, racing heart	57% positive response* for parent-rated ABC Hyperactivity subscale vs. 25% on placebo.
<i>Serotonin Reuptake Inhibitors</i>						
Citalopram	King, et al., 2009 ¹⁴⁸	Repetitive behavior	2.5-20 mg per day (mean 16 mg /day)	149 children 5-17 yo	Hyperactivity, insomnia, inattention, impulsivity, diarrhea, stereotypy	No significant difference in repetitive behavior on CGI-I and CY-BOCS PDD
Fluoxetine	Hollander, et al., 2005 ¹⁴⁹	Repetitive behavior	2.4-20 mg/day (mean 9.9 mg/day)	39 children 5-17 yo	None significant	Statistically significant decrease in repetitive behavior on CY-BOCS compulsions scale
Clomipramine	Gordon, et.al., 1993 ¹⁵⁰	Stereotypy, Repetitive behavior, Compulsions	25-250 mg / day (mean 152)	12 children 6-18 yo	Insomnia, constipation, twitching, tremors	Decrease in repetitive behavior on CPRS
	Remington et al., 2001 ¹⁵¹	Stereotypy, Irritability, Hyperactivity	100-150 mg per day (mean 128.4 mg/day)	31 subjects less than 20 yo	Lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea	No significant difference in stereotypy, irritability, or hyperactivity for clomipramine on the ABC.
<i>Stimulants</i>						
Methylphenidate	RUPP, 2005 ¹⁵² ,	Hyperactivity	7.5-50 mg per day divided tid	58 children 5-14 yo	Decreased appetite, insomnia, irritability,emotionality	49% positive responders* for hyperactivity vs. 15.5% on placebo
	Pearson, et al., 2013 ¹⁵³	Hyperactivity Inattention	10-40 mg qam, methylphenidate extended release	24 children 7-12 yo	Decreased appetite, insomnia	Significant decrease in hyperactivity & inattention on multiple teacher & parent measures
	Handen, et al., 2000 ¹⁵⁴	Hyperactivity	0.3-0.6 mg/kg/dose, bid-tid	13 children 5-11 yo	Social withdrawal, irritability	8 of 13 children with a >50% decrease in hyperactivity on the Teacher Connors Hyperactivity

Agent	Study	Target Symptoms	Dose	Demographics	Significant Side Effects	Primary Outcome(s)
	Quintana, et al., 1995 ¹⁵⁵	Hyperactivity	10-20 mg bid	10 children 7-11 yo	Irritability, anorexia, insomnia	Decrease in ABC Hyperactivity subscale by 8 points > placebo
<i>Miscellaneous</i>						
Amantadine	** King, et al., 2001 ¹⁵⁶	Hyperactivity, Irritability	2.5-5.0 mg per kg per day	39 children 5-19 yo	Insomnia	No statistical difference in parent ABC Hyperactivity or Irritability sub scales, statistical improvement in clinician Hyperactivity and Inappropriate Speech subscales.
Cyproheptadine (in combination with haloperidol)	Akhondzadeh, et al., 2004 ¹⁵⁷	ABC Total Score CARS	Titrated up to 0.2 mg/kg per day	40 children 3-11 yo	None significant, trend toward increased appetite	Statistically significant difference in ABC – Total score and CARS diagnostic screening tool, with unknown clinical significance.
Donepezil	Chez, et al., 2003 ¹⁵⁸	“Autistic Behavior” Expressive-Receptive Communication	1.25-2.5 mg per day	43 children 2-10 yo	Diarrhea, stomach cramping, irritability	“ Autistic behavior ” statistically, improved on CARS diagnostic screening tool with unknown clinical significance.
Naltrexone	Willemsen-Swinkels, et al., 1995 ¹⁵⁹	“Social Behavior” Irritability	Single 40 mg dose	20 children 3-7 yo	Sedation, Increased stereotypy	No effect on social behavior Significant reduction in ABC Irritability compared to placebo.
	** Kolmen, et al., 1995 ¹⁶⁰	Hyperactivity Communication initiation	1 mg per/kg per day	13 children 3-8 yo	Transient sedation	No significant difference in communication initiation
	** Feldman, et al., 1999 ¹⁶¹	Communication	1 mg/kg per day	24 children, 3-8 yo	Transient sedation	No significant difference in multiple communication measures.
	Campbell, et al., 1990 ¹⁶²	CGI CPRS Discriminant learning Hyperactivity	0.5-1 mg/kg per day	18 children 3-8 yo	Increased aggression and stereotypy	No significant difference in the CGI or CPRS or discriminant learning . Positive trend for hyperactivity
	Campbell, et al., 1993 ¹⁶³	Hyperactivity Discriminant learning Self-injurious behavior	0.5-1 mg/kg per day	41 children 3-8 yo	None significant	Significantly reduced hyperactivity ; no effect on discriminant learning . Positive

Agent	Study	Target Symptoms	Dose	Demographics	Significant Side Effects	Primary Outcome(s)
Pentoxifylline (in combination with risperidone)	Akhondzadeh, et al., 2010 ¹⁶⁴	Irritability, Hyperactivity, Stereotypy, Social withdrawal Inappropriate speech	200-600 mg per day	40 children 4-12 yo	Sedation, GI effects, increased appetite	trend for self-injurious behavior Significant improvement on the ABC Irritability and Social Withdrawal subscales

* A positive response in this study was defined as a >25% reduction in the ABC subscale and a Much Improved or Very Much Improved rating on the CGI-I.

** Study identified as funded by pharmaceutical industry.

*** A positive response in this study was defined as a >25% reduction in the C-YBOCS compulsions score and a Much Improved or Very Much Improved rating on the CGI-I.

TABLE 6: Resources for Parents

ASPEN TM, Inc.: (Asperger Syndrome Education Network) (<http://www.aspenj.org>) A regional non-profit organization providing families and those individuals affected with Asperger Syndrome and related disorders with information, support and advocacy.

ASC-US: (Asperger Syndrome Coalition of the US) (<http://www.asperger.org>) A national non-profit organization providing families and those individuals affected with Asperger Syndrome and related disorders with information, support and advocacy.

Autism Society of America: (<http://www.autism-society.org>) The mission of the Autism Society of America is to promote lifelong access and opportunities for persons within the autism spectrum and their families to be fully included, participating members of their communities through advocacy, public awareness, education, and research related to autism.

Autism Speaks: (<http://www.autismspeaks.org>) Autism Speaks is an autism science and advocacy organization, dedicated to funding research into the causes, prevention, treatments and a cure for autism; increasing awareness of autism spectrum disorders; and advocating for the needs of individuals with autism and their families.

Division TEACCH: (Treatment and Education of Autism and related Communication handicapped Children, University of North Carolina at Chapel Hill) (<http://www.unc.edu/depts/teacch>) The TEACCH website includes information about their program, educational and communication approaches to teaching individuals with autism, their research and training opportunities, as well as information and resources on autism.

Learning Disabilities Association of America: (<http://www.ldanatl.org>) The LDAA site includes information and resources on many learning disabilities, including learning disabilities involving a significant social component, such as autism and Asperger Syndrome.

OASIS: (Online Asperger Syndrome Information and Support) (<http://www.udel.edu/bkirby/asperger>) General information on Asperger syndrome and related disorders, including resources and materials, announcements of major pertinent events and publications, as well as being the major “intersection” for communication among parents, clinicians and educators, and individuals with social disabilities.

Yale Child Study Center: (www.autism.fm) Information on autism, Asperger syndrome, and related disorders, lists of resources organized by state, as well as parent support organizations and advocacy agencies.