JAMA | Review

Autism Spectrum Disorder
A Review

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IMPORTANCE Autism spectrum disorder (ASD), characterized by deficits in social communication and the presence of restricted, repetitive behaviors or interests, is a neurodevelopmental disorder affecting approximately 2.3% children aged 8 years in the US and approximately 2.2% of adults. This review summarizes evidence on the diagnosis and treatment of ASD.

OBSERVATIONS The estimated prevalence of ASD has been increasing in the US, from 1.1% in 2008 to 2.3% in 2018, which is likely associated with changes in diagnostic criteria, improved performance of screening and diagnostic tools, and increased public awareness. No biomarkers specific to the diagnosis of ASD have been identified. Common early signs and symptoms of ASD in a child's first 2 years of life include no response to name when called, no or limited use of gestures in communication, and lack of imaginative play. The criterion standard for the diagnosis of ASD is a comprehensive evaluation with a multidisciplinary team of clinicians and is based on semistructured direct observation of the child's behavior and semistructured caregiver interview focused on the individual's development and behaviors using standardized measures, such as the Autism Diagnostic Observation Schedule-Second Edition and the Autism Diagnostic Interview. These diagnostic measures have sensitivity of 91% and 80% and specificity of 76% and 72%, respectively. Compared with people without ASD, individuals with ASD have higher rates of depression (20% vs 7%), anxiety (11% vs 5%), sleep difficulties (13% vs 5%), and epilepsy (21% with co-occurring intellectual disability vs 0.8%). Intensive behavioral interventions, such as the Early Start Denver Model, are beneficial in children 5 years or younger for improvement in language, play, and social communication (small to medium effect size based on standardized mean difference). Pharmacotherapy is indicated for co-occurring psychiatric conditions, such as emotion dysregulation or attention-deficit/hyperactivity disorder. Risperidone and aripiprazole can improve irritability and aggression (standardized mean difference of 1.1, consistent with a large effect size) compared with placebo. Psychostimulants are effective for attention-deficit/hyperactivity disorder (standardized mean difference of 0.6, consistent with a moderate effect size) compared with placebo. These medications are associated with adverse effects including, most commonly, changes in appetite, weight, and sleep.

CONCLUSIONS AND RELEVANCE ASD affects approximately 2.3% of children aged 8 years and approximately 2.2% of adults in the US. First-line therapy consists of behavioral interventions, while co-occurring psychiatric conditions, such as anxiety or aggression, may be treated with specific behavioral therapy or medication.

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by social communication impairments and restricted, repetitive behaviors (Box 1).[1,2] ASD consists of a spectrum of symptoms reflecting impaired social communication and restricted, repetitive behaviors and ranges in severity from mildly impairing to severe (Table 1). It is recognized as a collection of related disorders of different etiologies. Manifestations of ASD are heterogeneous and can include individuals with intellectual disability and limited language ability and those with significantly above-average intellectual and language function who have difficulty with social communication. These difficulties manifest in the pragmatics or social norms associated with communication, such as speaking with appropriate volume, interacting at appropriate physical distance, and detecting and adapting communication in response to gestures and facial expression. Rigidity, manifested by requiring others to speak or behave in specific ways or needing to adhere to prescribed schedules or activities, is common. The complexity and heterogeneity of ASD are related to both developmental factors, such as age and IQ, and environmental factors, such as availability of support including individualized educational services and speech, language, and behavioral interventions. Intellectual disability, language disorder and medical and psychiatric conditions, including

Box 1. Diagnostic Criteria for Autism Spectrum Disorder (ASD) Based on *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, Text Revision[a]

To meet diagnostic criteria for ASD according to DSM-5, a child must have persistent deficits in each of 3 areas of social communication and interaction (see A.1. through A.3. below) plus at least 2 of 4 types of restricted, repetitive behaviors (see B.1. through B.4. below).

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see below):
   1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior. (See below.)

A. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):
   1. Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (eg, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
   3. Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
   4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (eg, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior. (See below.)

A. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).
B. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
C. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) 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.

Note: Individuals with a well-established *DSM-IV* diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of ASD. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for ASD, should be evaluated for social (pragmatic) communication disorder.

Specify if:
- With or without accompanying intellectual impairment
- With or without accompanying language impairment (Coding note: use additional code to identify the associated medical or genetic condition.)
- Associated with another neurodevelopmental, mental, or behavioral disorder (Coding note: use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)
- With catatonia
- Associated with a known medical or genetic condition or environmental factor

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epilepsy, sleep problems, anxiety, and depression, are common.[3,4] This review summarizes current evidence regarding the epidemiology, pathophysiology, diagnosis, and clinical management of ASD.

Methods

We searched PubMed for English-language studies of the epidemiology, etiology, pathogenesis, diagnosis (screening and assessment), and treatment of ASD published from January 1, 2010, to October 31, 2022. We manually searched the references of selected publications for additional relevant articles. When selecting papers to include, randomized clinical trials, systematic reviews, meta-analyses, clinical practice guidelines, and articles relevant to a general medical readership were prioritized. Of 591 publications identified, 46 articles were included, consisting of 11 randomized clinical trials, 6 cohort studies, 5 systematic reviews, and 24 meta-analyses. The effect sizes reported in this review consist of standardized mean difference (SMD), also known as Cohen *d*, unless otherwise specified. An SMD of 0.2 to 0.5 indicates a small effect, 0.5 to 0.8 indicates a medium effect, and greater than 0.8 indicates a large effect.

Discussion

Epidemiology

Among children aged 8 years in the US, the estimated prevalence of ASD has increased from approximately 1.1% in 2008 to 2.3% in 2018.[5] Studies that use administrative databases (eg, special

Table 1. Severity Levels for Autism Spectrum Disorder[a]

Severity level	Social communication	Restricted, repetitive behaviors
Level 3: requiring very substantial support	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. For example, a person with few words of intelligible speech who rarely initiates interaction and, when they do, makes unusual approaches to meet needs only and responds to only very direct social approaches.	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.
Level 2: requiring substantial support	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 responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	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.
Level 1: requiring support	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

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education data, health records) tend to underestimate the prevalence of ASD compared with studies that use more rigorous methods for case ascertainment, such as a total population sampling and standardized screening and diagnostic measures.[6,7]

Changes in diagnostic criteria, increased awareness of ASD, improved ascertainment, and greater access to services, such as early behavioral intervention and education with individualized programs designed for children with ASD, have likely contributed to the higher prevalence of ASD.[8,9] In addition, the definition of autism now includes a broader spectrum, which may partially explain the increase in prevalence over earlier estimates.

The estimated prevalence of ASD is higher in males than in females (3.7% [95% CI, 3.5-3.8] in boys and 0.9% [95% CI, 0.8-0.9] in girls aged 8 years in the surveillance conducted by the Autism and Developmental Disabilities Monitoring Network in 11 states in the US).[5] Studies that used rigorous methods for case ascertainment reported lower male-to-female ratios of the estimated prevalence of ASD: 3.7% (95% CI, 2.6-4.9) in boys and 1.5% (95% CI, 0.6-2.4) in girls.[9] Girls and women are more likely or better able to minimize ASD symptoms, including social communication difficulties (clinically referred to as "camouflaging").[10] It is also possible that current diagnostic procedures are less sensitive to the presence of ASD among females.[11] A study using a large database of 641 860 adults residing in the community reported higher ASD rates in transgender and gender-diverse individuals compared with cisgender individuals.[12] Children with ASD who are Black tend to present at older ages than those who are White and more often present with intellectual disability,[5] suggesting racial disparities in access to care.[13]

In a study of 664 children with ASD in which younger siblings were followed up prospectively from birth, 19% of these younger siblings were diagnosed with ASD by the age of 36 months.[14] Rates of diagnosis of ASD were 14% in male siblings compared with 5% in female siblings in an observational study of 39 460 children with ASD using an administrative database.[15]

Pathogenesis and Pathophysiology

In population-based data sets from 3 Nordic countries that collectively included 22 156 people with ASD and studied mean estimated heritability, the variation in ASD traits attributed to genetic factors was 81% (95% CI, 74%-85%).[16] Environmental factors were associated with 14% to 22% of the risk of ASD in the same study. A relatively small number of rare genetic variants in approximately 100 genes (eg, *KMT2A*, *NRXN1*, *SHANK3*) have been identified that were associated with significant risk,[17] whereas a larger number, perhaps thousands, of common variants were associated with smaller risk but, in combination, accounted for the majority of cases.[18,19] Genetic risk factors for ASD overlap with other diverse developmental and psychiatric disorders.[16,20,21] A variety of genetic and environmental factors have been associated with ASD, but none are absolutely specific for the development of ASD.

Many of the autism risk genes affect gene expression regulation, neurogenesis, chromatin modification, and synaptic function. Additional support for the role of genetic factors was reported by Willsey et al.[22] This study used an in vivo *Xenopus* model and examined 10 genes with the strongest statistical association with ASD that all were expressed in the telencephalon (the forebrain that is primarily composed of the cerebral hemispheres) at time points corresponding to human mid-prenatal prefrontal cortex development.[22] Estrogen mitigates the effects of ASD risk gene disruption, and this may help explain the sex differences in prevalence.

A meta-analysis of studies identified that maternal factors, such as gestational hypertension (odds ratio, 1.4 [95% CI, 1.2-1.5]), overweight before or during pregnancy (relative risk [RR], 1.3 [95% CI, 1.2-1.4]), preeclampsia (RR, 1.3 [95% CI, 1.2-1.5]), and maternal age of 35 years or older (RR, 1.3 [95% CI, 1.2-1.5]) were associated with higher rates of ASD in offspring (absolute rates not provided).[23] In addition, cohort and case-control studies reported that advanced paternal age (21% increase in ASD diagnosis in offspring for every 10-year increase in paternal age),[24] medication use in pregnancy, and

Box 2. Early Behavior Signs of Possible Autism Spectrum Disorder

Absence of Developmentally Expected Milestone Attainment

Avoids or does not maintain eye contact.

Does not respond to name by 9 months of age.

Does not show facial expressions of emotions by 9 months of age.

Rarely shares enjoyment with caregivers.

No simple interactive games (eg, pat-a-cake) by 12 months of age.

Uses no or few gestures (eg, does not wave goodbye).

Does not share interests with others.

Does little or no imitation of other people or does not pretend.

No pointing (to show caregivers something interesting) by 18 months of age.

Emergence of Aberrant Behaviors

Lines up toys in a particular order and gets upset when the order is changed.

Uses repetitive words and phrases.

Moves their fingers, hands, or body in an unusual way (finger flicking, hand flapping, body rocking, spinning self in circles, for example).

Shows excessive interest in particular objects.

Has obsessive interests in certain objects and attachment to unusual objects.

Has unusual reactions to sensory stimuli (eg, getting upset about a clothing tag, avoiding eating food with certain textures).

Has strong interest in and seeks unusual sensory experiences (eg, squinting or flapping hands to certain lights, excessively rubbing certain textures, licking or smelling objects.).

both short (<12 months) and long (≥72 months) periods between pregnancies[25] were associated with an increased risk for the diagnosis of ASD in offspring. Regarding medication use during pregnancy and risk of ASD, the absolute risk for ASD for offspring was 4.4% (95% CI, 2.6%-7.5%) with exposures to valproic acid during pregnancy compared with the risk of 1.5% (95% CI, 1.5%-1.6%) for ASD without exposure to valproic acid in a population-based study of 655 615 children in Denmark.[26] Although selective serotonin reuptake inhibitor (SSRI) use during pregnancy has been associated with an increased risk for ASD in cohort studies, a meta-analysis underscored that the association was confounded by other factors, especially the indication for SSRI use and the genetic association between maternal depression and risk for ASD.[27] Therefore, evidence does not preclude the use of SSRIs for treating depression during pregnancy when indicated. A large body of research refutes claims of linkage between vaccines and ASD.[28-30]

Clinical Presentation

The presenting symptoms of ASD depend on age, language levels (from nonverbal to fully fluent), cognitive abilities, and sex. In the first 2 years of life, common features include poor acquisition of or declines in language skills and communicative gestures or failure to learn or adopt these skills. ASD is also characterized by diminished responsiveness in social interactions and presence of repetitive behaviors, such as no response to name when called, hand flapping, and lining up toys in a particular way (Box 2).[31-33]

Behavioral or cognitive rigidity (eg, insisting that routines are precisely followed or that others adhere to specific verbal scripts), lack of interest in socializing, restricted interests, and lack of imaginative play typically become more apparent as a child develops. Children with visual and/or hearing impairment may have delays in attaining developmental milestones (eg, deficits in nonverbal communication due to blindness) compared with those without sensory impairment and exhibit behaviors that overlap with ASD symptoms (eg, stereotyped, repetitive motor movements),[34] requiring careful assessment to determine whether behaviors these children exhibit are part of the symptoms of ASD. The estimated prevalence of ASD is higher in individuals with special health needs. For example, the estimated prevalence of ASD is 19% in people with visual impairment, 9% in people with hearing impairment,[35] 18% in people with intellectual disability,[36] 16% in people with Down syndrome,[37] and 30% in people with fragile X syndrome.[37]

Children who have ASD that is not associated with delays in acquiring language or other developmental milestones may experience delays in diagnosis of ASD. These individuals may first come to receive medical attention because of behavioral problems associated with ASD, such as disruptive behaviors, difficulties following instructions due to intense interest in preferred activities, or co-occurring neurodevelopmental and psychiatric disorders. Individuals without moderate or severe intellectual or learning disability may seek professional evaluation in adulthood if they encounter challenges obtaining or sustaining education or employment and have characteristics of ASD.[38]

Co-occurring developmental and psychiatric conditions are common in people with ASD. Other neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and intellectual disability, are more likely to co-occur in people with ASD compared with those without ASD (28% vs 7% for ADHD and 23% vs 0.7% for intellectual disability).[3,39,40] Anxiety and depressive disorders also co-occur more frequently in people with ASD than those without ASD (20% vs 7% for anxiety disorder and 11% vs 5% for depressive disorders).[3] In older children, adolescents, and adults, coexistent mood disorders and related behaviors (eg, depression and suicidality) may greatly contribute to reduced quality of life and increased mortality.[41] Severe behaviors, such as aggression and self-injury, may occur with ASD.[42] People with ASD are at increased risk of specific medical conditions, such as epilepsy (21% in people with ASD and intellectual disability and 8% in those without intellectual disability vs 0.8% in ageneral population sample),[43,44] feeding problems (eg, focus on specific foods, sensitivity to textures),[45] motor coordination difficulties such as trouble coordinating movements between the left and right side of the body or problems maintaining their posture (37% vs 5%),[46,47] gastrointestinal conditions (eg, constipation [22%]),[48] and sleep difficulties (13% vs 5%)[3] compared with those without ASD. These conditions may bring children to medical attention and lead to a diagnosis of ASD.[4]

Savant skills, defined as special skills that exceed what conventionally seems humanly possible, most commonly manifest in memory, art, music, mental arithmetic, and calendar calculation (eg, the ability to provide the day of the week for any given date going back hundreds of years)[49] are more common in people with ASD. People with extreme savant skills may capture media attention, but may provide stereotyped portrayals of ASD. Savant skills may occur in as many as approximately 29% of affected individuals.[50] Some

features of ASD, such as restricted interests and repetitive behaviors, may predispose to intense focus and relentless practice of skills that eventually become superior.[49,51]

Diagnosis of ASD

Screening

The American Academy of Pediatrics recommends that all children be screened at 18 and 24 months of age for ASD.[52] In contrast, in 2016 the US Preventive Services Task Force concluded that evidence was insufficient to recommend screening for ASD in young children for whom no concerns were raised by their parents because of a lack of randomized clinical trials that addressed the question of whether early identification of ASD in young children through screening could improve core symptoms of ASD.[53] The US Preventive Services Task Force called for additional research on whether earlier identification through universal screening is associated with improved outcomes in children with ASD to update the statement issued in 2016.[54]

The Modified-Checklist for Autism in Toddlers, Revised (M-CHAT-R), a 20-item screening questionnaire, is one of the frequently used autism-specific screening tools in primary care settings designed to identify children aged 16 to 30 months who are at risk for ASD from a general population.[55] Children whose M-CHAT-R total score is higher than 2 are considered at risk for ASD and require follow-up questions by health care professionals for additional information about the items the child did not pass on the M-CHAT, which increase its specificity (sensitivity of 85% and specificity of 99% for the M-CHAT-R with follow-up questions). Guidelines generally do not recommend one autism-specific screening tool over others. Children who have a positive screening test result for ASD should undergo a comprehensive evaluation and referral for developmental services, consisting of early behavioral intervention and family guidance. There is no evidence to support screening for ASD in asymptomatic adults, and few screening tools for ASD exist for adults.[55] The National Institute for Health and Care Excellence in the UK recommends that clinicians consider using the Autism Spectrum Quotient, a 10-item screening tool, for adults with suspected ASD who do not have moderate or severe intellectual disability to determine whether a referral for a comprehensive assessment is indicated.[38]

Diagnostic Assessment

The criterion standard for an ASD diagnosis is the best-estimate clinical consensus, defined as agreement within a multidisciplinary professional team based on a detailed developmental history and observation of the individual's behaviors using standardized diagnostic tools. The most widely used of these standardized diagnostic tools for ASD include the Autism Diagnostic Interview, Revised (ADI-R), a semi-structured interview with the parent(s), and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), a semi-structured direct observation of a child's behavior. The diagnostic conclusion incorporates definitions from the *Diagnostic and Statistical Manual of Mental Disorders* and *International Classification of Diseases* as well as the diagnostic impression and opinions from multidisciplinary professionals involved in the assessment.[42] The ADI-R and the ADOS-2 have sensitivity of 80% (95% CI, 79%-82%) and 91% (95% CI, 90%-92%), respectively. Specificity is 72% (95% CI, 70%-74%) for the ADI-R and 76% (95% CI, 74%-78%) for the ADOS-2.[56] Nevertheless, these diagnostic tools should inform and not supersede clinical judgement. Cognitive and adaptive function testing, such as the Differential Ability Scales, Wechsler Intelligence Scale for Children, and Vineland Adaptive Behavior Scales, and assessment of speech and language to evaluate quantitative and qualitative speech abilities and communication skills are important for establishing the diagnosis of ASD as well as developing therapy plans. Sensory and motor assessments can provide useful supplementary information related to functional fine and gross motor skills and sensory processing differences (eg, sensory hypersensitivity and hyposensitivity).[57] Multidisciplinary assessment can assist clinicians in differentiating between ASD and other disorders (eg, intellectual disability, pragmatic language disorder, ADHD). ASD diagnostic tools are not standardized in individuals with visual impairment and hearing loss. Co-occurring emotional and behavioral problems may also affect performance on diagnostic measures for ASD.[58]

The American Academy of Pediatrics and the American College of Medical Genetics and Genomics recommend genetic testing for individuals who are diagnosed with ASD.[42,52,59] Ascertaining a genetic etiology of ASD through genetic testing can provide patients, families, and clinicians with information about recurrence risk and prognosis and help navigate patients and families to support and resources specific to genetic conditions. In particular, chromosomal microarray is recommended to scan the genome for copy number variants. Fragile X testing is recommended for all individuals diagnosed with ASD, and females with developmental regression should be tested for Rett syndrome (MECP2 gene sequencing). Clinicians should consider referring the patient to a geneticist if ASD associated with a genetic syndrome is suspected based on family history and congenital anomalies, such as craniofacial anomalies or macrocephaly, on physical examination. The detection of potentially causal genetic abnormalities can inform family planning discussions and subsequent medical surveillance. However, the probability of clinically actionable findings from testing must be balanced by the potential financial or physical burden of testing on patients.

Individuals with established ASD benefit from thorough physical examinations given high rates of gastrointestinal problems, such as constipation and abdominal discomfort; dermatological conditions, such as atopic dermatitis; and neurological manifestations in certain genetic disorders, such as tuberous sclerosis complex. An electroencephalogram is not recommended as part of the evaluation for ASD unless there are concerns about epilepsy or specific developmental disorders associated with abnormal encephalographic findings (eg, Landau-Kleffner syndrome, which is characterized by aphasia and agnosia).[42]

Management

The goal of therapy is to improve an individual's function and well-being.[60] Behavioral interventions are well-supported by evidence (eg, see the National Standards Project by the National Autism Center[61]). No medications have demonstrated efficacy for the core diagnostic symptoms of ASD.[62,63] Pharmacologic interventions, such as aripiprazole and risperidone, can mitigate behavioral and emotional dysregulation that co-occur in individuals with ASD. Current evidence is summarized for psychosocial interventions in Table 2 and for pharmacological interventions in Table 3. Box 3 highlights some commonly asked questions regarding clinical care for individuals with ASD.

Table 2. Therapeutic Interventions for Individuals With Autism Spectrum Disorder (ASD)

Therapy type	Appropriate age range for therapy	Target condition(s)	Description of therapy	Summary of evidence
Behavioral approaches (eg, early intensive behavioral intervention [EIBI], Discrete Trial Training)	Young children (aged <5 y)	Adaptive skills, cognition, language, motor skills, social communication, and emotional and behavioral disorders	Intensive, individualized behavior analytic approaches, where antecedents of (environments leading to) behaviors and functions of behaviors are analyzed through behavior observation to build new repertoires and reduce interfering behaviors.	The pooled effect size of intensive behavioral therapy (approximately 25 h/w) in a meta-analysis of 21 studies, including both RCTs and quasi-experimental studies was small to medium: 0.24 (95% CI, 0.01-0.47) for language, 0.29 (95% CI, 0.05-0.54) for cognitive ability, 0.38 (95% CI, 0.19-0.56) for adaptive behavior, and 0.40 (95% CI, 0.18-0.61) for social communication.[64]
Developmental approaches (eg, Developmental, Individual-Differences, Relationship-Based/ Floortime model, Preschool Autism Communication Trial)			Social-pragmatic approaches intended to promote social communication and interactions. In this model, development is considered to be the result of children's active exploration of their physical and social surroundings.	A meta-analysis of 11 RCTs demonstrated that developmental approaches were associated with improved social communication (effect size, 0.27 [95% CI, 0.05-0.48]), but not language effect size, 0.06 (95% CI, −0.08 to 0.21).[64]
Naturalistic Developmental Behavioral Intervention (NDBI) (eg, ESDM, pivotal response training, JASPER, Project ImPACT)			An approach integrating both behavioral and developmental principles: the NDBI approaches emphasize the developmental systems approach and are diverse from the EIBI in a way that instructions and teaching are delivered in a physical environment that looks similar to typical daily experiences.	A meta-analysis of 17 RCTs of people with ASD showed that, compared with control/behavioral interventions commonly available in the community, the NDBIs were associated with better developmental outcomes, including language (effect size, 0.21 [95% CI, 0.01-0.41]), play (effect size, 0.33 [95% CI, 0.13-0.54]), and social communication (effect size, 0.42 [95% CI, 0.23-0.62]) domains.[64] In a randomized clinical trial of 87 participants, the effect of 2 different treatment intensities (15 h/wk for 12 mo vs 25 h/wk for 12 mo) of the ESDM, one of the NDBIs did not significantly differ on the intervention outcomes, including autism severity, expressive communication, receptive language, and nonverbal development.[65]
Treatment and Education of Autistic and Related Communication Children (TEACCH)	Children, adolescents, and adults	ADL, language, communication, social skills, executive functioning, and engagement	Emphasizes a close working relationship between parents and practitioners, adapts the intervention to the particular characteristics of the individual client, and makes use of structured teaching experiences. TEACCH is one of the most widely used approaches in school settings.	A meta-analysis of 6 studies (4 quasi-experimental studies and 2 RCTs) of 202 participants showed no significant association of TEACCH with improvement in social communication outcomes (effect size, −0.11 [95% CI, −0.93 to 0.71]).[65] However, the lack of benefit was likely due to a noncluster randomized design used in the RCTs and the lack of studies with large sample sizes.
Psychotherapy (cognitive behavioral therapy [CBT])	School-age children, adolescents	Anxiety	CBT is based on the cognitive model, in which people's behaviors and emotions are influenced by their perceptions of events. In CBT for anxiety, imaginal and in-vivo exposure tasks are essential, in addition to identifying cognition in anxiety-provoking situations and developing cognitive reappraisal. The focus of CBT is problem-oriented, with an emphasis on the present.	In a meta-analysis of 45 RCTs and 6 quasi RCTs of 2485 participants with ASD, the effect size of CBT on social-emotional problems in individuals with ASD was statistically significant, but was associated with a modest effect (effect size, 0.57 [95% CI, 0.24-0.90]).[66] In a 16-wk RCT of 167 children aged 6-13 y, adapted CBT for ASD (90-min weekly with parental involvement) was significantly better for reducing anxiety symptoms compared with generic CBT (effect size, 0.63 [95% CI, 0.27-0.99]) and treatment as usual/non-CBT psychotherapy commonly available in the community (effect size, 1.69 [95% CI, 1.10-2.26]).[67] Studies targeting adults with ASD are scarce but emerging.[68]
Group social skills interventions (GSSIs)	Adolescents, young adults	Social skills	Group interventions with a manual providing strategies to foster social competence, including direct instruction with written or visual materials, modeling, role-play, and group sessions.	In a meta-analysis of 9 RCTs with 362 participants with ASD, UCLA PEERS, the most widely used manual-based GSSI for ASD, consisting of 12 90-min sessions delivered once a week, was associated with an increase in self-reported social knowledge (effect size, 2.15 [95% CI, 1.54-2.77]) and parent-reported social functioning at week 12 (effect size, 0.71 [95% CI, 026-1.15]) compared with the delayed-treatment control group.[69] In the RCTs included in the meta-analysis, the delayed-treatment control group received UCLA PEERS intervention after the postintervention assessment was conducted at wk 12.

Abbreviations: ESDM, Early Start Denver Model; JASPER, Joint Attention, Symbolic Play, Engagement, and Regulation; PEERS, Program for Excellence in Education and Research in the Sciences; Project ImPACT, Project Improving Parents as Communication Teachers; RCT, randomized clinical trial.

Table 3. Pharmacological Interventions for Individuals With Autism Spectrum Disorder (ASD)

Medication by condition	Category of medication and mechanism of action	Strength of evidence[a]	Common adverse events[b]
Irritability, aggression, emotional dysregulation			
Aripiprazole	Atypical antipsychotics; partial agonist at D_2 dopamine receptor and serotonin (5-HT)1A receptors and an antagonist at serotonin 5-HT2A receptor.	In a meta-analysis of 5 RCTs and 808 children and adolescents with ASD, aripiprazole was associated with a reduction of emotional dysregulation, including irritability and aggression compared to placebo (SMD, 1.18; 95% CI, 0.84 to 1.52).[70]	Drowsiness ,10.4% (vs 3.96% in the placebo group); vomiting, 13.6% (vs 5.94%); increased appetite, 9.43% (vs 6.93%); and extrapyramidal symptoms 8.96% (vs 3.96%)
Risperidone	Atypical antipsychotics; Antagonist at D_2 dopamine receptor and 5-HT2A receptors but has a higher affinity for 5-HT2A receptors than for D_2 receptors. Adrenergic and histaminergic receptors are also involved in its mechanism of action.	In a meta-analysis of 6 RCTs and 372 participants with ASD, risperidone was associated with improvement in irritability and emotional dysregulation compared with placebo (SMD, 1.07 [95% CI, 0.82-1.33]).[70]	Drowsiness, 40.0% (vs 8.0% in the placebo group); vomiting, 17.3% (vs 16.0%); constipation, 14.0% (vs 6.40%); increased appetite, 40.7% (vs 16.8%); and extrapyramidal symptoms 16.0% (vs 8.0%)
ADHD			
Methylphenidate (MPH)	Psychostimulant medication; blocks the reuptake of dopamine and noradrenaline through the blockade of dopamine and noradrenaline transporters.	In a meta-analysis of 4 placebo-controlled RCTs and 117 children with ASD, MPH was associated with a reduction of ADHD symptoms (SMD, 0.60 [95% CI, 0.23-0.96] for parent-rated overall ADHD symptoms).[71] All 4 studies used a crossover study design, and study duration was short (1-2 wk).	Appetite decrease, 29.8% (vs 9.65% in the placebo group); sleep problems, 27.2% (vs 2.91%); irritability, 21.1% (vs 17.5%); headache, 6.14% (vs 1.75%); and stomach discomfort, 9.65% (vs 1.75%)
Atomoxetine	Nonpsychostimulant ADHD medication; inhibits the presynaptic noradrenaline transporter and prevents the reuptake of noradrenaline.	Atomoxetine, compared with placebo, was associated with improvement in ADHD symptoms (SMD, 0.44 [95% CI, 0.06-0.93]) in a meta-analysis of 4 RCTs with 237 children with ASD.[71]	Appetite decrease, 43.0% (vs 22.5% in the placebo group); irritability, 33.6% (vs 34.9%); sleep problems, 30.5% (vs 17.8%); and vomiting, 25% (vs 14.7%)
Extended-release guanfacine	Nonpsychostimulant ADHD medication; stimulates postsynaptic α_{2A}-adrenergic receptors to enhance noradrenaline neurotransmission.	The effectiveness of extended-release guanfacine is supported by evidence from an 8-week placebo-controlled RCT (n = 62) for improvement in the investigator-rated total ADHD symptoms (SMD, 1.20 [95% CI, 0.66-1.75).[72]	Drowsiness, 86.7% (9.4% in the placebo group); decreased appetite, 43.3% (vs 6.25%); emotional/tearful, 40% (vs 3.1%); and dry mouth 40% (vs 3.1%)
Restricted, repetitive behaviors			
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline)	Antidepressants; inhibit the serotonin transporter at the presynaptic axon terminal and inhibit the reuptake of serotonin, thereby increasing the availability of serotonin in the synapse.	In a meta-analysis of 7 RCTs and 631 participants, SSRIs overall were not associated with improvement in restricted, repetitive behaviors in ASD (effect size, 0.09 [95% CI, −0.21 to 0.39]).[73]	Gastrointestinal problems, 16.1% (vs 11.3% in the placebo group); mood disturbance, 28.7% (vs 23.7%); energy increase, 30.5% (vs 16.5%); insomnia, 31.1% (vs 25.3%); and vivid dreams 8.42% (vs 0%)
Anxiety and depression		No RCTs conducted specifically to examine the efficacy of SSRIs for mood and anxiety symptoms in individuals with ASD.	
Sleep problems			
Melatonin	Other; activates melatonin receptors with a high affinity for the melatonin 1 receptor, thereby regulating the sleep/wake cycle.	In a 13-wk RCT comparing prolonged-release melatonin and placebo in 125 children (96.8% had ASD; 3.2% had Smith-Magenis syndrome), melatonin increased total sleep time by 51.2 min vs 18.7 min in the placebo group ($P = .03$; Cohen $d = 0.4$) and decreased sleep latency by 37.9 min vs 12.6 min in the placebo group ($P = .01$; Cohen $d = 0.5$).[74]	Somnolence, 28.3% (vs 10.8% in the placebo group), headache 13.3% (vs 6.2%)
Hyperactivity, irritability			
N-Acetylcysteine (NAC)	Other; functions as an antioxidant through its contribution to the production of glutathione, a major intracellular antioxidant within the central nervous system.	In a meta-analysis of RCTs (5 trials, 225 individuals with ASD), NAC, compared with placebo, was associated with a significant reduction in hyperactivity (mean difference, 4.80 [95% CI, 1.20-8.40]) and irritability (mean difference, 4.07 [95% CI, 1.13-7.01]), but there were no differences between these 2 groups in overall changes in social communication and stereotyped behavior.[75]	GI symptoms, 32.3% (vs 20.6% in the placebo group) and drowsiness, 12.9% (vs 6.5%)
Social communication challenges			
Oxytocin	Other; neuropeptide potentially plays an important role in modulating social-communicative behaviors.	Despite initial positive findings in small sample-sized trials, oxytocin failed to demonstrate efficacy in improving social communication compared with placebo (least square mean change, −3.7 [95% CI, −4.8 to −2.8] vs −3.5; [95% CI, −4.4 to −2.6]; $P = .61$) in the largest sample-sized RCT with 290 children and adolescents with ASD.[76]	Increased appetite, 16% (vs 10% in the placebo group); increased energy, 10% (vs 3%); and restlessness 8% (vs 2%)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; RCT, randomized clinical trial; SSRI, selective serotonin reuptake inhibitor.

[a] A standardized mean difference (SMD) of 0.2 to 0.5 indicates a small effect, 0.5 to 0.8 indicates a medium effect, and greater than 0.8 indicates a large effect.

[b] Adverse events listed here can occur in a general population and are not specific to individuals with ASD.

Box 3. Commonly Asked Questions About Autism Spectrum Disorder (ASD)

Among Adults Presenting for the First Time With Possible ASD, What Other Conditions Should Be Considered in the Differential Diagnoses?

Individuals who present in adulthood with a neurodevelopmental disorder typically have symptoms that are mild, have developed strategies to minimize the effects of social communication difficulties, and do not have obvious repetitive behaviors.
The differential diagnosis generally includes anxiety disorders (eg, social anxiety), obsessive compulsive disorder (restricted or repetitive behaviors), social pragmatic disorder (awkward social communication), and perhaps attention-deficit/hyperactivity disorder (inattention and impulsivity leading to poor social relationships). All of these diagnoses may coexist with ASD, which adds to the diagnostic complexity for adults presenting for the first time with possible ASD.

Are There Special Considerations in General Medical Care for Individuals With ASD?

People with ASD who have limited communication ability and coexisting medical conditions (eg, infections, constipation, pain) may present with behavioral problems, including aggression or self-injurious behaviors (head-banging, self-hitting). Additionally, adverse effects from medications prescribed for physical problems, including anticonvulsants for epilepsy, can exacerbate behavioral problems. Abrupt changes in behavior may indicate underlying disease.

Are There Accommodations That Can Improve Interactions With Health Care Clinicians During Outpatient Medical Appointments With Patients Who Have ASD?

It can be helpful to discuss specific strategies to achieve improved outcomes with family or caregivers in advance of an appointment (eg, managing sensory sensitivities, transitions, or specific fears). Scheduling patients with ASD at the beginning or end of the day can reduce time in the waiting room, which can be particularly stressful for patients with ASD. It may be helpful for some individuals to have a preclinic visit to see the setting and meet staff prior to presenting for examination.

What Are Evidence-Based Treatment Options for Individuals With ASD?

Behavioral interventions early in life are effective for improving social communication and interaction and reducing problem behaviors, which can be used across the lifespan. Emotional and behavioral problems, such as anxiety, aggression, or attention-deficit/hyperactivity disorder associated with ASD can be mitigated by cognitive behavioral therapy and pharmacotherapy.

Behavioral Interventions

Early intervention based on well-established behavioral analytic principles has focused primarily on young children, but can be used in people of any age to help them acquire specific skills and address problem behaviors across the lifespan. These principles focus on attaining behavior change based on understanding and manipulating predisposing environmental conditions or events that may reinforce specific behaviors after they occur. In general, therapies are more effective for improving symptoms associated with ASD, such as using language effectively, than for features of ASD such as impairment in social communication and repetitive, restricted patterns of behaviors. The Naturalistic Developmental Behavioral Interventions involve the use of applied behavior analytic principles of learning with a focus on teaching children developmentally appropriate skills in natural settings (eg, play, routine activities).[77] The Naturalistic Developmental Behavioral Interventions were associated with an improvement in children's language, play, and social communication in a meta-analysis that included 16, 7, and 17 randomized clinical trials, with effect sizes of 0.2 (95% CI, 0.1-0.4), 0.3 (95% CI, 0.1-0.5), and 0.4 (95% CI, 0.2-0.6), respectively.[64] At least 25 hours per week of these interventions is recommended to achieve optimal developmental outcomes,[78] but a 2021 randomized clinical trial of 87 participants did not demonstrate differences in the composite scores of the intervention outcomes, including autism severity (P = .80), expressive communication (P = .36), receptive language (P = .96), and nonverbal abilities such as fine motor skills and daily living skills (P = .54), between therapies with different intensities (15 hours/week for 12 months vs 25 hours/week for 12 months).[65] Parent-mediated intervention, consisting of joint attention therapy (therapy focusing on improving skills to share focus on an object or area with another person, such as finger pointing to look at something and making eye contact with someone when sharing an experience), social communication therapy, and behavioral therapy, delivered by trained parents is currently under evaluation as a potential treatment.[79] In a meta-analysis of 19 randomized clinical trials, parent-delivered interventions were associated with significant, but relatively small, improvement in ASD symptom severity (effect size, 0.2 [95% CI, 0.03-0.4]), socialization (effect size, 0.2 [95% CI, 0.09-0.4]), and cognition (effect size, 0.2 [95% CI, 0.03-0.5]).[80]

School-age children diagnosed with ASD generally have access to behavioral, speech, occupational, and physical therapies in the school setting. The inclusion of children in general education classrooms with visual support strategies (visual cues, such as a picture of a child placing a sweater on a coat hook at the entrance to a classroom, or social scripts, such as a short text that outlines what a child can expect during a visit to the doctor) to prompt and reinforce positive social behaviors can promote adaptive behaviors.[81] Treatment and Education of Autistic and Related Communication-Handicapped Children is one of the well-established educational programs characterized by highly structured work routines and visual presentation of information to facilitate acquisition of learning goals from individualized schedules that are based on each person's learning characteristics, skills, and strengths.[82]

Approximately 20% of people with ASD have anxiety and approximately 11% have depression. Anxiety and depression can interfere with adaptive functioning and well-being.[83] Cognitive behavioral therapy (CBT) is a first-line treatment for these conditions in individuals with ASD.[84] In a 16-week randomized clinical trial for 167 children with ASD aged 6 to 13 years, CBT adapted for ASD (90 minutes weekly with parental involvement) was superior to treatment as usual (ie, non-CBT services) in reducing anxiety symptoms (Cohen d, 1.7 [95% CI, 1.1-2.3]).[67] However, few randomized clinical trials have studied CBT for depression in people with ASD.[68] In children and adolescents with ASD who have no or mild cognitive impairment, social deficits and poor friendship quality typically worsen during adolescence when social skills may not be developed enough to meet social demands.[85] Providing people with ASD with social skills training delivered in a group format is associated with modest effects on social competence.[86] Effective therapies

are needed to help people with ASD succeed in postsecondary education and the work environment.[87,88]

Pharmacological and Other Biomedical Interventions

Risperidone and aripiprazole, which have dopaminergic and serotonergic antagonistic effects, are currently approved by the US Food and Drug Administration for irritability and aggression in patients with ASD (Table 3). Although their efficacy is supported by meta-analyses of randomized clinical trials, the medications have adverse effects that include hyperglycemia, dyslipidemia, and weight gain. The effect size of risperidone, compared with placebo, for the outcome of irritability and aggression was 1.10 (95% CI, 0.8-1.3) in a meta-analysis of 372 participants with ASD and the effect size of aripiprazole, compared with placebo, was 1.20 (95% CI, 0.8-1.5) in a meta-analysis of 808 participants with ASD. Psychostimulants (methylphenidate) and nonpsychostimulants (atomoxetine and guanfacine) were effective for managing ADHD symptoms in ASD. For example, in a meta-analysis of 4 clinical trials including 97 participants with ASD, compared with placebo, methylphenidate had an effect size of 0.6 (95% CI, 0.2-1.0) for hyperactivity symptoms,[71] and in a meta-analysis of 4 clinical trials including 204 people with ASD, compared with placebo, atomoxetine had an effect size of 0.5 (95% CI, 0.2-0.8) for hyperactivity symptoms.[71] In a randomized clinical trial of 62 people with ASD, compared with placebo, extended-release guanfacine had an effect size of 1.2 (95% CI, 0.7-1.8) for overall ADHD symptoms. However, people with both ADHD and ASD are more likely to experience behavioral activation, consisting of restlessness and disinhibition, with psychostimulants compared with individuals without ASD.[71] Melatonin may be useful for sleep problems in people with ASD.[89] In a randomized clinical trial of 125 children and adolescents in which 97% of participants had ASD, prolonged-release melatonin, compared with placebo, increased sleep duration by 32 minutes (P = .03; effect size, 0.4) and reduced sleep-onset latency by 25 minutes (P = .01; effect size, 0.5).[74] Fluoxetine, an SSRI, did not improve obsessive-compulsive behaviors compared with placebo in a 16-week clinical trial of 146 children and adolescents (effect size, −0.38 [95% CI, −0.76 to −0.004]).[90] Similarly, in a meta-analysis of 7 randomized clinical trials that included 519 people, SSRIs overall were not associated with reduced restricted, repetitive behaviors in ASD (effect size, 0.1 [95% CI, −0.2 to 0.4]).[73]

Because of the lack of effective pharmacotherapies for ASD, families are frequently interested in complementary and alternative approaches. Some supplements, such as N-acetylcysteine[75] and sulforaphane,[91] have been studied in randomized clinical trials and demonstrated efficacy for emotional and behavioral symptoms. However, current evidence does not support any supplement for ASD symptoms of speech delay, poor social interaction, or restricted or repetitive behaviors.[75,91] In a randomized clinical trial of 150 children and adolescents with ASD that compared cannabis extract–containing cannabidiol with tetrahydrocannabinol administered in a 20:1 ratio (whole-plant cannabis extract), purified cannabinoid-containing cannabidiol and tetrahydrocannabinol administered in a 1:1 ratio (pure cannabinoid), and placebo, changes in the primary outcome of the child's noncompliant behavior at home did not differ among the 3 groups. However, the whole-plant cannabis extract significantly improved disruptive behaviors, a second primary outcome, compared with placebo (49% responder rate vs 21% responder rate; P < .01), while pure cannabinoids did not differ from placebo in the same measure (38% responder rate vs 21% responder rate; P = .08).[92]

ASD in the Clinic/Office Setting

Adults with ASD are more likely to report lower satisfaction with patient-clinician communication[93] and have lower health care self-efficacy[94] in the general clinic setting than adults without ASD. People with ASD are more likely to visit the emergency department for medical care than people without ASD.[95] A cross-sectional analysis of the Nationwide Emergency Department Sample database on emergency department visits from the years 2006 to 2011, data that were created for the Healthcare Cost and Utilization Project, reported that adults with ASD were more likely to have a psychiatric visit (15% vs 4.2%; P < .01) as well as an injury visit (16.1% vs 13.6%; P < .01) compared with adults without ASD.

The Academic Autism Spectrum Partnership in Research and Education, a project funded by the National Institutes of Health, developed a health toolkit for adults with ASD and their primary care physicians[96] and provides physicians with information to improve care. Examples include giving patients extra time to answer questions, scheduling longer appointments, using natural or dim light in the examination room, and ensuring that the examination room is quiet and calming.

Transitions of care between pediatric and adult medicine are important, because those with ASD may have difficulty finding adult clinicians familiar with ASD when they become too old for pediatric practices.[97] A national survey of 56 014 people with special health care needs revealed that only 23% of youth (individuals aged 12-17 y) with ASD received health care transition services to improve their health care knowledge and encouraged independent management of their health care needs in transitioning from pediatric to adult services, compared with 50% for youth with other special health care needs.[98]

Prognosis

With respect to social, psychological, and health outcomes, adults with ASD less frequently live independently, are more frequently unemployed, and have higher needs and higher use of mental health services than people without ASD.[99] Better cognitive abilities during childhood are associated with higher levels of independence, education, and employment later in life, but are not associated with higher rates of friendship or well-being reported by caregivers.[100]

Premature mortality rates are approximately 2-fold higher for individuals with ASD than for the general population.[101] Mortality risk in people with ASD is increased by the coexistence of neurologic disorders, such as seizure (mortality rates of 1.1% vs 0.2%), and co-occurring mental/behavioral disorders, such as mood disorders (mortality rates of 0.4% vs 0.2%).[102] Suicide attempts and death by suicide are more common in individuals with ASD than in the general population. In a population-based study of 6 559 266 people in Denmark,[103] incident rates for suicide attempts were 266 per 100 000 person-years in people with ASD and 63 per 100 000 person-years in those without ASD (incident rate ratio after adjusting for sex, age, and period, 3.2 [95% CI, 2.9-3.5]). Similarly, incident rates for death by suicide were 24 per 100 000 person-years in people with ASD and 14 per 100 000 person-years in those

without ASD (incident rate ratio after adjusting for sex, age, and period, 3.8 [95% CI, 2.9-4.9]).

Limitations

This review has several limitations. First, the search was restricted to English-language publications. Second, the quality of included literature wasnot formally evaluated. Third, some relevant papers may have been missed.

Conclusions

Autism spectrum disorder affects approximately 2.3% of children aged 8 years and 2.2% of adults in the US. First-line therapy consists of behavioral interventions delivered bya multidisciplinary team, while co-occurring mental health conditions, such as anxiety or aggression, may be treated with specific behavioral therapy or medications.

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