Autism Spectrum Disorder

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Sharon M. Griffin, RN, PhD, specializes in Health Education and Chronic Disease Management especially as it relates to her primary areas of study and research. She has more than 30 years of healthcare experience nationwide and is an accomplished author, presenter and consultant. She frequently lectures on the subjects of Attention Deficit/Hyperactivity Disorder (AD/HD), Obsessive-Compulsive Disorder (OCD) and related disorders. Dr. Griffin is the cofounder of the University Center for Assessment and Learning (UCAL) of Andrews University in Berrien Springs, Michigan. She enjoys writing and teaching and has been listed in Who's Who in American Nursing, Two Thousand Notable American Women, and the eleventh edition of the World Who's Who of Women, Cambridge, England.

Faculty Disclosure

Contributing faculty, Sharon M. Griffin, RN, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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A complete Works Cited list begins on page 26.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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NetCE designates this continuing education activity for 5 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 1 pharmacotherapeutic/pharmacology contact hour.

AACN Synergy CERP Category A.

Social Workers participating in this intermediate to advanced course will receive 5 Clinical continuing education clock hours.

NetCE designates this continuing education activity for 2 NBCC clock hours.

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Individual State Behavioral Health Approvals

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

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Course Objective

Autism spectrum disorder (ASD) has a significant impact on daily functioning and quality of life and has significant morbidity and disability associated with severe cases. However, it often goes unrecognized and is commonly underdiagnosed. The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ASD. Additionally, this course will provide the information necessary to screen children seen in primary care for ASD in order to appropriately refer patients and their families for more expansive assessment and treatment referral as rapidly as possible in order to avoid unnecessary morbidity and mortality.

Learning Objectives

Upon completion of this course, you should be able to:

1. Review the epidemiology of autism spectrum disorder (ASD).
2. Discuss the theories of autism etiology and pathophysiology.
3. Discuss components of screening for and diagnosing autism, including the impact of comorbidities on ASD diagnosis and treatment.
4. Identify the goals of treatment for children with ASD.
5. Discuss the classes of evidence-based interventions and characteristics of effective treatments for ASD.
6. Outline the role of pharmacotherapy in the management of ASD.
7. Discuss the impact of ASD on the family.
8. Review the prognosis of individuals diagnosed with ASD.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

For several decades after the first description of autism in 1911, children with autism were thought to have emotional problems or to suffer from a type of schizophrenia. In 1938, the Austrian pediatrician Hans Asperger identified a similar syndrome, with social or emotional impairment as the core feature, that he termed "autistic psychopathy," and in 1944, he published a comprehensive study on the topic [1]. Asperger's observations did not become widely known until 1981, and the syndrome was not included in medical diagnostic manuals until 1994 [1].

Autism spectrum disorder (ASD) is now understood to be a neurodevelopmental disorder that affects communication and behavior. Although ASD can be diagnosed at any age, it is classified as a developmental disorder because symptoms generally appear in the first two to three years of life [2]. ASD is identified as a "spectrum" disorder because it is characterized by wide variation in the type and severity of symptoms that each individual experiences [3]. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), people with ASD have difficulty with communication and interpersonal interactions, restricted interests and repetitive behaviors, and symptoms or behaviors that interfere with the individual's ability to function properly at school, at work, and in all other areas of life [2].

The independent diagnoses of autistic disorder, atypical autism, Asperger disorder, childhood autism, childhood disintegrative disorder, early infantile autism, high-functioning autism, Kanner autism, and pervasive developmental disorder not otherwise specified have been in common use for some time; however, these subtypes have largely been abandoned in favor of a diagnosis that reflects the current understanding of autism. Individuals with one of these previously established diagnoses, and any new cases, will now generally be given a diagnosis of ASD [4]. The goal of the spectrum

diagnosis is to make a diagnosis of ASD less subjective and more specific, in order to correctly exclude those who do not have ASD while correctly identifying and including those who do [5]. The DSM-5 also separates the behavioral criteria from medical conditions that may underlie the cause for the behavioral symptoms of ASD.

There has been debate about whether the new diagnostic criteria and the rediagnosis of patients using the new criteria will create gaps in treatment or problems with insurance coverage, but the unreliability of the older criteria necessitated a change. Studies have shown that most patients (91%) with a previously diagnosed pervasive developmental disorder are subsequently diagnosed with ASD [6].

EPIDEMIOLOGY

Autism is the most common neurodevelopmental disorder in the United States. Estimates of the prevalence of ASD suggest that as many as 400,000 individuals in the United States have ASD or a related condition [7]. In the United States, ASD prevalence is 1 in 44 children at 8 years of age and is 4.2 times more common among boys than girls, with male-to-female prevalence ratios ranging from 33.3:1 to 5.2:1 [7; 8; 176]. Prevalence estimates are nearly identical for non-Hispanic white, non-Hispanic black, and Asian/Pacific Islander children (18.5, 18.3, and 17.9 per 1,000 population, respectively) but lower for Hispanic children (15.4) [8]. Black children with ASD are less likely to have a first evaluation by 36 months of age than are white children with ASD (40% versus 45%). The overall median age at earliest known ASD diagnosis (51 months of age) is similar by sex and by racial and ethnic groups [8]. Reported rates of ASD have been rising in many countries over the past two decades. Based on a review of epidemiologic studies, the global prevalence of ASD is estimated to be 7.6 cases per 1,000 population [9].

In 2015, the direct and indirect costs of caring for children and adults with ASD in the United States were estimated to be $268 billion, more than the cost of stroke and hypertension combined [10]. Lost productivity for caregivers of an individual with ASD averages $18,720 per year [11]. One study found that ASD is associated with approximately $3.6 million in lifetime social costs that could be mitigated by identifying known modifiable risk factors [12].

ETIOLOGY: RESEARCH AND THEORIES

Like ASD itself, the theories of autism are diverse and often overlapping. It was once believed that poor parenting caused autism. The terms "refrigerator mother" or "refrigerator parents" were used to describe emotionally frigid parents who were thought to be too distant, cold, and uncaring to allow the child to bond properly. This view has been referred to as the psychogenic theory of autism; however, it remains unsupported by the scientific and medical communities.

The final common pathway theory proposes that the causes of autism all share the characteristic of damage in regions of the brain responsible for the development of typical communication, social functioning, and play [13]. Contemporary researchers have coined the term connectivity theory to describe atypical communication between regions of the brain [14]. The connectivity referenced is generally functional connectivity, or the degree to which synchronized activity occurs between brain regions. By examining connectivity patterns while participants rest in a brain scanner, researchers report that autism is sometimes characterized by underconnectivity between distant brain regions, sometimes by overconnectivity between neighboring ones, and sometimes by differences in connectivity within certain brain networks [14].

The signaling imbalance theory of autism suggests that the condition arises from a hyperexcitable brain [15]. Balanced brain signaling occurs when glutamate and gamma-amino butyric acid (GABA) operate in sync, allowing brain cells to be active in some circumstances and muted in others. Brain hyperactivity may contribute to the repetitive behaviors and motor difficulties characteristic of autism and also might contribute to social dysfunction, although this connection is less direct [15].

The predictive coding theory (also called predictive processing or the Bayesian brain) holds that brains generate a model of the world that predicts what one sees, hears, touches, smells, and tastes [16]. According to this theory, brains of persons with autism either do not form accurate predictions or sensory input is overridden by the internal predictive models. Predictive coding may account for the social, sensory, and other difficulties of autism [16].

The biologic theory of autism holds that various medical conditions, including gene mutations and/or infections or environmental exposures in genetically predisposed individuals, cause ASD [3]. Studies of have found that certain medical conditions occur with greater frequency in children with ASD than in children without autism. When autism occurs in conjunction with a medical condition that is capable of damaging the nervous system, the medical condition is typically assigned as the cause of autism. Medical conditions that are commonly identified with autism include [17; 18; 19; 20]:

- Fragile X syndrome
- Tuberous sclerosis complex (TSC)
- Congenital rubella
- Herpes encephalitis
- Abnormalities of carbohydrate metabolism
- Moebius syndrome
- Leber congenital amaurosis (an eye disorder)

While the definitive causes of ASD remain unknown, research has focused on obstetric complications, infection, genetics, vaccinations, and parental age [7].

OBSTETRIC COMPLICATIONS

Research suggests that adverse events during the prenatal and perinatal periods and during delivery may place infants at increased risk of ASD. Some of the factors associated with increased ASD risk include hypertension or diabetes in the mother, threatened abortion, gestational age ≤36 weeks, spontaneous labor, induced labor, pre-eclampsia, and fetal distress [21].

The authors of one study compared the frequency of prenatal/perinatal factors among 323 children with ASD, 257 of their unaffected siblings, and 1,504 typically developing controls, and investigated the effects of the factors on the severity of autistic symptoms. Results indicated that the children with ASD and their unaffected siblings had more prenatal/perinatal events than did the typically developing controls, with higher numbers of events in the children with ASD than in their unaffected siblings. Additionally, the events were associated with greater stereotyped behaviors, social-emotional problems, socio-communication deficits, and overall ASD severity. Six prenatal/perinatal events (pre-eclampsia, polyhydramnios, oligoamnios, placenta previa, umbilical cord knot, and gestational diabetes) were associated with the severity of autistic symptoms, particularly stereotyped behaviors and socio-communication deficits [22].

The authors of another study sought to estimate the prevalence of ASD in 899 children, 10 years of age, who were born extremely preterm (23 to 27 weeks gestational age) between 2002 and 2004 [23]. The children were first evaluated with the Autism Diagnostic Interview-Revised (ADI-R). Those who met the ADI-R criteria were then assessed with the Autism Diagnostic Observation Schedule-2 (ADOS-2). A positive ADOS-2 score was the criterion for ASD. Twenty-six participants were not assessed for ASD because of severe sensory or motor impairment. Sixty-one children in the remaining sample met the criteria for ASD, resulting in an overall prevalence of 7.1%. ASD

risk decreased with increasing gestational age, from 15.0% at 23 to 24 weeks, to 6.5% at 25 to 26 weeks, to 3.4% 27 weeks [23].

Several studies of one of the largest population-based datasets (nearly 6 million live births) found that children conceived using artificial reproductive technology (ART) were twice as likely to be diagnosed with autism [24]. The exact association is unclear, although the higher likelihood of adverse pregnancy and delivery outcomes with ART are suspect (e.g., twin birth, low birth weight, prematurity).

Although a number of birth and pregnancy complications have been associated with autism, alone they are unlikely to cause the condition. It is more likely that they either operate in combination with other factors or are indications of existing abnormalities [13; 25].

INFECTION

Infections that damage the brain during fetal development or childhood and that have been associated with autism include [17; 18; 26; 27; 28; 29; 30; 31; 32]:

- Rubella: The rubella virus may damage the fetal brain and result in severe birth defects known as the congenital rubella syndrome (CRS) when infection occurs early in pregnancy. Rubella infection and CRS are now rare in the United States due to widespread vaccination. However, studies have found that rubella vaccines do not elicit a strong immune response in many women and that, even in strong responders, subclinical reinfection is possible, as vaccine-induced immunity is significantly less protective than natural immunity. Epidemiologic studies have found no association between rubella vaccination and autism. Some evidence suggests that altered vitamin A metabolism, which precipitates rubella infection, causes CRS through maternal liver dysfunction and exposure of the fetus to excessive vitamin A, which is a known teratogen.
- Cytomegalovirus (CMV): CMV infection may result in mental handicap/disability/deficit and, more rarely, autism. However, many newborn children who have been exposed to CMV have no apparent problems. While maternal CMV seropositivity is associated with more severe ASD symptoms in children, a direct role for the virus has yet to be determined.
- Herpes encephalitis: The herpes virus can sometimes infect an infant's brain, leading to encephalitis. Occasionally, children who develop herpes encephalitis display an autistic-like condition; however, a definitive role of HSV on the onset of ASD has yet to be determined.

Findings from a 2019 study indicate that fetal exposure to maternal infection that requires hospitalization increases the child's risk for ASD and depression later in life [33]. A population-based cohort study of nearly 1.8 million Swedish children born between 1973 and 2014 were observed for up to 41 years. In the cohort, exposure to maternal infection in pregnancy significantly increased the child's risk for ASD and depression. Estimates for ASD and depression were similar following a severe maternal infection. The hazard ratio following a urinary tract infection was 1.89 for ASD and 1.30 for depression [33].

Maternal infection and fever during pregnancy were evaluated using data from the Study to Explore Early Development (SEED), a case-control study of children 2 to 5 years of age, born between 2003 and 2006 in the United States. The study explored a possible association between maternal infection and fever during pregnancy and risk of ASD and other developmental disorders (DDs) [34]. The study included three groups of children: 606 with ASD, 856 with a DD, and 796 from the general population, randomly sampled from state birth records. Telephone interviews with the mother as well as maternal prenatal and labor/delivery medical records provided information about infection and fever during pregnancy. ASD and DD status were determined by an in-person

standardized developmental assessment of the child at 3 to 5 years of age. After adjustment for covariates, maternal infection anytime during pregnancy was not associated with ASD or DDs. However, second trimester infection accompanied by fever elevated the risk for ASD approximately twofold, suggesting that the inflammatory response to the infectious agent may be relevant [34].

FAMILIAL/GENETIC FACTORS

Autism occurs more frequently in some families than in others. Published estimates of sibling recurrence for ASD range from 6.9% to 19.5% [35; 36]. Six hundred sixty-four infants with an older biological sibling with ASD were followed from early in life to 36 months of age, when they were classified as either having or not having ASD, after receiving a clinical diagnosis from an expert clinician. In this study, 18.7% of the infants developed ASD, with infant gender and having more than one older affected sibling being significant predictors of ASD outcome. Male infants had a threefold increased risk of ASD, and infants with more than one older affected sibling had a twofold increased risk of ASD [37]. Additionally, in some families of children with autism, researchers have identified parents who may have undiagnosed ASD [17; 38]. This is not surprising given that ASD and related subclinical traits show familial clustering, which supports the role of genetic factors in the architecture of ASD [39; 40; 41; 42; 43]. Researchers have identified dozens of copy number variant loci and ASD-relevant genes and loci, many of which overlap those associated with other neurodevelopmental disorders [44; 45].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Medical Genetics and Genomics recommends a genetic consultation be offered to all persons/families with autism spectrum disorders. Evaluations should be considered for any individual along the entire autism spectrum.

(https://www.acmg.net/PDFLibrary/Austism-Spectrum-Genetics-Evaluation.pdf. Last accessed December 18, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

Studies of twins have demonstrated a moderate genetic heritability for ASD and a substantial shared twin environmental component [46]. In studies of twins in which at least one of the twins has a disability, researchers have found that the rate of both identical twins having autism is significantly higher than the rate in nonidentical twins. Studies have also indicated that identical twins have a concordance rate for ASD between 36% and 95%. The rate for nonidentical twins is 0% to 31% [17; 47; 48].

VACCINATIONS

In the early 1990s, the number of autistic diagnoses was steadily rising. Some believed this to be an epidemic, which pointed to a toxin or other environmental factor as the cause of autism. This perceived epidemic coincided with a change in the childhood vaccine schedule. Some parents of children with autism, along with certain grassroots organizations and researchers, turned their focus to vaccines. They believed that a link existed between autism and vaccines, specifically the preservative, thimerosal.

Thimerosal is 49.6% ethyl mercury, a known neurotoxin [49]. It has been used safely since the 1930s to prevent the contamination of vaccines [50; 51]. By 1999, thimerosal was used in more than 30 vaccines in the United States. Although the amount of thimerosal used in each vaccine was less than the amount considered toxic by the Environmental Protection Agency (EPA), when the amounts from all of the required vaccinations for infants were added together, the sum exceeded the safe level [52]. An early study by the Centers for Disease Control and Prevention (CDC) suggested a possible connection between the amount of thimerosal given and certain neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD), speech and language delays, and tics. However, further review led many to feel that this study was flawed [50].

In 1999, the American Academy of Pediatrics (AAP) and the U.S. Public Health Service recommended removing thimerosal from vaccines due to the cumulative exposure risk [53]. However, this was mainly done as a precautionary measure to reduce the population's heavy metal exposure wherever possible, not in response to a known effect. By 2001, all vaccines that were routinely recommended for children in the United States had available alternatives without thimerosal [51].

The Institute of Medicine (IOM) convened several committees to examine the evidence and determine if there was a causal relationship between autism and thimerosal [54; 55]. The eighth and final report, published in 2004 by the IOM Immunization Safety Review Committee, concluded that the evidence favored rejection of a causal relationship between thimerosal-containing vaccines and autism [56]. A study of the prevalence of autism in California children, conducted from 1995 to 2007, found that autism rates had continued to increase after thimerosal was eliminated from most childhood vaccines. These results supported the IOM conclusion that thimerosal is not a primary cause of autism [57]. However, some researchers, using the same government data, discovered an overall decrease in neurodevelopmental disorder diagnoses following the removal of thimerosal from vaccines [58]. A 2013 study conducted by the CDC looked at the number of antigens from vaccines during the first two years of life and found that the total amount of antigen from vaccines received was the same between children with ASD and those without ASD [59].

PARENTAL AGE

Advanced paternal age has been suggested as a risk factor for autism, but the evidence for such an association is mixed. One meta-analysis examined the association while controlling for documented autism risk factors (e.g., family history, perinatal conditions, infant characteristics, demographic variables) [60]. Multiple study methods were adopted, including a birth cohort and a family analysis of siblings discordant for autism. The meta-analysis also included population-based epidemiologic studies. In the birth cohort, autism risk increased with increasing paternal age. The offspring of men 50 years of age and older were 2.2 times more likely to have autism than the offspring of men 20 years of age and younger. The family analysis of discordant siblings showed that affected siblings had older paternal age, after adjusting for maternal age and parity [60].

THE PATHOPHYSIOLOGY OF ASD

Neuroimaging studies of patients with ASD reveal abnormal cellular configurations in several regions of the brain, including the frontal and temporal lobes and the cerebellum. Enlargements of the amygdala and the hippocampus are common in childhood. Magnetic resonance imaging (MRI) studies have provided evidence for differences in neuroanatomy and connectivity, specifically reduced or atypical connectivity in frontal brain regions and thinning of the corpus callosum in both children and adults with ASD. Some of the regional differences correlate significantly with the severity of specific autistic symptoms. Similarly, region-specific differences in concentrations of gray matter have been found [7].

Observed reductions in brain GABA (a naturally occurring amino acid and neurotransmitter) are believed to contribute to the sensorimotor and behavioral anomalies manifest in ASD [61; 62]. Glutathione, the brain's primary antioxidant, makes its impact through the process of oxidative stress, which in turn may play a role in the pathogenesis and pathophysiology of ASD [63].

Children with ASD have discreet reductions in plasma levels of cysteine, glutathione, and methionine; reductions in the ratio of the enzymes *S*-adenosyl-L-methionine (SAMe) to *S*-adenosyl-L-homocystein (central to the regulation of many biologic processes); and reductions in the ratio of reduced to oxidized glutathione (an antioxidant capable of preventing damage to cellular components) [64]. Reduced concentrations of

N-acetylaspartate (NAA) (a metabolite generally abundant in the central nervous system) have been associated with cognitive dysfunction, diminished neuronal activity, and reduced cellular oxidative metabolism. Reduced NAA has been found to diminish neuronal metabolism in boys with ASD in contrast to age-matched controls [62; 65]. Metabolic anomalies (e.g., elevated blood serotonin, reduced serum biotinidase), impaired mitochondrial function, and neural inflammation also have been identified in some people with ASD [64; 66].

SCREENING AND DIAGNOSIS

The DSM-5 divides the characteristics of ASD into two core domains: social communication/social interaction and restricted/repetitive patterns of behavior [4; 67]. Delays in or absence of the development of spoken language is common in autism. In some instances, language begins to develop appropriately and then seems to stop suddenly. Approximately 25% of children with ASD will have a regression in language or social skills, typically between 18 and 24 months of age [68; 69].

Other features of ASD include [7]:

- Developmental regression (13% to 48% of children with ASD have apparently typical development until 15 to 30 months of age, when they lose verbal/nonverbal communication skills)
- The absence of protodeclarative pointing (e.g., using the index finger to indicate an item of interest to another person)
- Unusual responses to environmental stimuli (e.g., screaming at certain sounds)
- The absence of typical responses to pain and physical injury
- The absence of symbolic (make-believe) play
- Vulnerability to infections and febrile illnesses

Developmental screening can be done by a number of healthcare professionals. Those who screen should be uniquely positioned to identify symptoms of ASD early in childhood, support the family through the processes of diagnosis and intervention, and promote the child's developmental health. ASD can sometimes be detected as early as 18 months of age, and by 2 years of age, diagnosis by an experienced professional is considered very reliable. Early diagnosis is critical to providing timely treatment [70].

The AAP recommends that all children be screened for developmental delays and disabilities during regular well-child visits at 9, 18, and 30 months of age, with additional screening as needed for children at high risk for developmental problems due to preterm birth or low birth weight. Additionally, all children should be screened specifically for ASD with a standardized tool at 18 and 24 months of age, with ongoing developmental surveillance [10; 71]. Developmental surveillance for ASD includes asking caregivers about any concerns they have about their child's development or behavior, informal observation, and monitoring of symptoms in the context of routine health supervision [10].

The American Academy of Child and Adolescent Psychiatry recommends that the developmental assessment of young children (including infants) and the psychiatric assessment of all children should routinely include questions about ASD symptomology [72]. Guidelines developed by the American Academy of Neurology (AAN) and the Child Neurology Society also recommend that developmental surveillance be performed (using recommended screening tools) at all well-child visits, beginning at infancy and continuing through school-age, and that the evaluations be repeated any time concerns about the child's developmental progress are raised (i.e., not meeting developmental milestones) [73]. Developmental screening tools recommended by the AAP and AAN include the Ages and Stages Questionnaire, the BRIGANCE Early Childhood Screens, the Child Development Inventories, and the Parents' Evaluations of Developmental Status [72; 73].

BEHAVIORAL CUES INDICATING THE NEED FOR REFERRAL TO A SPECIALIST	
Behavior	**Age**
No babbling, pointing, or other gestures	By 12 months of age
No single words	By 16 months of age
No two-word, spontaneous (nonecholalic) phrases	By 24 months of age
Any lack of developmentally-appropriate language or social skills	At any age
Source: [73]	*Table 1*

DSM-5 CRITERIA FOR ASD AND EXAMPLES		
Domains	**Criteria: Deficits**	**Examples[a]**
Persistent deficits in social communication, social interaction across multiple contexts, as manifested by criteria in this domain (currently or by history, must have all three symptoms in this domain)	Social-emotional reciprocity	Abnormal social approach and failure of normal back-and-forth conversation Reduced sharing of interests, emotions, or affect Failure to initiate or respond to social interactions
	Nonverbal communicative behaviors used for social interaction	Poorly integrated verbal, nonverbal communication Abnormalities in eye contact and body language or deficits in understanding and use of gestures Total lack of facial expressions and nonverbal communication
	Developing, maintaining, understanding relationships	Difficulties adjusting behavior to suit various social contexts Difficulties sharing imaginative play or making friends; absence of interest in peers
Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history	Stereotyped or repetitive motor movements, use of objects, or speech	Simple motor stereotypies, lining up toys or flipping objects Echolalia Idiosyncratic phrases
	Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior	Extreme distress at small changes Difficulties with transitions Rigid thinking patterns Greeting rituals A need to take same route or eat the same food every day
	Highly restricted, fixated interests that are abnormal in intensity or focus	Strong attachment to or preoccupation with unusual objects Excessively circumscribed or perseverative interest
	Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment	Apparent indifference to pain/temperature Adverse response to specific sounds or textures Excessive smelling or touching of objects Visual fascination with lights or movement
[a]Symptoms must be present in 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. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning and are not better explained by intellectual disability or global developmental delay.		
Source: [10; 67]		*Table 2*

ASD SYMPTOMS BY LEVEL OF SEVERITY		
Severity Level	**Social Affective**	**Restrictive/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.	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.	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.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.
Source: [4]		*Table 3*

After considering the parent's assessment and clinical observations, the provider should assess a positive or negative screen for developmental delays. If specific behaviors are exhibited by the child (***Table 1***), immediate evaluation for autism should be performed using one of the validated screening instruments [73]. If the screening is positive for ASD, a standard psychiatric assessment should follow, including interviews with the child and family, a review of past records, and a full history [72].

A medical assessment also is necessary and typically includes a physical examination, a hearing screen, and genetic testing [72]. Psychologic tests, a communication assessment, and occupational/physical therapy evaluations also may be warranted [10].

The provider should discuss the importance of these assessments with the family, assist them in navigating through the process, and connect them with community and other resources. Families with low income or language barriers may require additional attention to take the next steps [10].

DIAGNOSTIC CRITERIA

To fulfill diagnostic criteria for ASD using the DSM-5, all three symptoms of social affective difference must be present, in addition to two of the four symptoms related to restrictive and repetitive behaviors (***Table 2***) [10; 67].

The DSM-5 also introduced an approach to severity rating that reflects the impairment of the ASD symptoms and resulting needs of the individual (***Table 3***) [10; 67]. Although attempts have been made to capture severity of core symptoms and allow for measurement of improvement with interventions, no single adequate measure has been established to date [74; 75].

EXAMPLES OF SYNDROMES/DISORDERS ASSOCIATED WITH ASD	
Condition	**Characteristics**
Fragile X syndrome	Intellectual disability, macrocephaly, large ears, large testicles, hypotonia, joint hyperextensibility
Tuberous sclerosis	Hypopigmented macules, CNS hamartomas, seizures, intellectual disability
Angelman syndrome	Global developmental delay, hypotonia, wide-based ataxic gait, seizures, progressive spasticity
Rett syndrome (primarily in girls)	Apparently typical development for first 5 months of life and normal head circumference at birth. Deceleration of head growth from 5 to 48 months, resulting in microcephaly. Loss of previously acquired hand skills, with onset of hand-wringing stereotypes. Seizures often develop.
Tourette syndrome	Tics seen in Tourette syndrome may appear similar to motor stereotypes associated with ASD. Children with Tourette syndrome usually lack social/communication impairments seen with ASD; however, social isolation may be a factor due to embarrassment or peer avoidance.
Landau-Kleffner syndrome	Loss of language comprehension and verbal expression. Child often appears to have acquired deafness; some children develop serious behavioral dysfunction, including hyperactivity, temper outbursts, or withdrawn behaviors, but rarely as severe as those seen with ASD.
Obsessive compulsive disorder (OCD)	The obsessive thoughts and repetitive actions seen in OCD can appear similar to the ritualistic behaviors and motor stereotypes seen in ASD.
Attention deficit-hyperactivity disorder (ADHD)	Children with ADHD may have impairments in social skills and may have difficulty sustaining conversation due to inattention. Likewise. children with ASD often have problems with hyperactivity, impulsivity, and inattention.
Cornelia de Lange syndrome	Growth delays, intellectual disability, and/or developmental delays and behavioral problems. Children also may have hearing impairment and abnormal speech development.
Prader-Willi syndrome (PWS)	All individuals with PWS have some cognitive impairment that ranges from low normal intelligence with learning disabilities to mild-to-moderate intellectual disability. Behavioral problems are common and can include temper tantrums, obsessive/compulsive behavior, and skin picking. Motor milestones and language development are often delayed.
Oppositional defiant disorder (ODD)	Behavior problems seen in children with ODD are usually intentional, whereas children with ASD are more likely to display behavior problems (e.g., tantrums) for no apparent reason.
Source: [4; 13; 76; 77; 78; 79]	*Table 4*

DIFFERENTIAL DIAGNOSIS OF ASD

Symptoms consistent with a diagnosis of ASD overlap significantly with a wide range of psychiatric and medical conditions. Accurate diagnosis of ASD is made difficult by the many differential diagnoses that should be considered in an individual presenting with the cognitive and behavioral symptoms of ASD [76]. Children with intellectual disability may have autistic features but not meet the criteria for ASD. Additionally, children with ASD may or may not have intellectual disability. It is important, therefore, that alternative diagnoses (***Table 4***) be firmly ruled out before an individual is diagnosed with autism [4; 13; 76; 77; 78; 79]. Signs of neglect or abuse, sensory problems, and speech/language disorder should be closely examined [10; 76].

SYMPTOMS OF COMORBID HEALTH ISSUES
Behaviors that May Indicate Underlying Illness
Sudden behavior change; change to appetite, dietary preferences
Loss of previously acquired skills
Irritability, low mood, tantrums, oppositional behavior; aggression
Heightened anxiety; avoidance behaviors
New repetitive movements
Hypersensitive to sensory input (e.g., sensitive to light, specific sounds)
Teeth grinding
Facial grimacing
Vocal moaning, groaning, sighing, whining
Common Sources of Pain[a]/Discomfort
Headache, earache, toothache
Sore throat
Reflux, esophagitis, gastritis, colitis
Soft or hard stool constipation (underlying cause is relevant)
Small intestinal bacterial overgrowth
Musculoskeletal injury or disease
Seizure disorder (including subclinical crisis)
Allergy disorder
[a]Pain can be acute or chronic, progressive or static.
Source: [87; 88; 94] *Table 5*

COMORBIDITIES

Many children and adults with ASD have comorbid health conditions. One retrospective study examined the comorbidity burden of ASD in more than 14,000 children and young adults across three general hospitals and one pediatric hospital [80]. Patients with autism had higher than expected rates of all of the medical conditions studied (e.g., eczema, allergies, gastrointestinal problems, seizures, asthma) compared with general patient populations of health centers [80]. Additional studies from the United States, Europe, and Asia confirmed the high prevalence of medical comorbidities among children and young adults with ASD [81; 82; 83; 84]. Medical comorbidities such as epilepsy, gastrointestinal conditions, and respiratory disorders are associated with a mortality rate that is 3 to 10 times higher among patients with ASD than in the general population [85; 86].

A consensus report published by the AAP states that, "care providers should be aware that problem behavior in patients with ASD may be the primary or sole symptom of the underlying medical condition" [87]. Further, "behaviors in the ASD population are often physical in origin, identifiable through investigation, and treatable or manageable through appropriate medical care" [88]. The AAP also encourages clinicians to listen to parents, because they generally give accurate and quality information [89]. However, like the clinicians who are working with communicatively impaired patients with ASD, parents or caregivers also may face communication barriers with the child. Furthermore, parents may be unaware of the possible implications of the symptoms, especially if they have been previously told that behaviors are simply autistic. Nearly one-third of adults with high-functioning autism report that they do not receive appropriate medical care for physical health problems [89].

Autism is increasingly recognized as a whole-body disorder, with the core characteristics commonly attributed to ASD now being attributed to manifestations of a systemic and complex disease process [88]. Study results are challenging the belief that ASD is static, lifelong, and unchangeable, with many results providing evidence that significant improvement is possible following intensive, individualized intervention [90; 91; 92; 93]. It is now established that "specific medical problems are associated with the severity of the condition and that successfully addressing these comorbidities often leads to significant improvement in overall functioning" [88].

Managing comorbid illness in the patient with ASD is challenging on many levels (e.g., communication deficits, processing pain or tenderness, lack of history), but can be improved with knowledge about the symptoms (***Table 5***) that manifest in the patient who presents with comorbid health issues [88].

SEIZURE DISORDERS

The prevalence of seizure disorders is high in people with ASD, and their co-occurrence with ASD contributes to an elevated mortality risk [95]. One meta-analysis of 19 studies found a pooled ASD prevalence of 6.3% in epilepsy. When divided by type, the risks of ASD for general epilepsy, infantile spasms, and focal seizures were 4.7%, 19.9% and 41.9%, respectively [95]. Individuals with epilepsy 18 years of age and younger were found to have a risk of ASD that was 13.2 times greater than that of individuals 18 years of age and older. Individuals with co-occurring intellectual disability had a risk for ASD that was 4.9 times higher than those without intellectual disability. Primary risk factors for epilepsy in patients with ASD include the presence of intellectual disability, female sex, age, and symptomatic etiology of epilepsy [95].

SLEEP DISORDERS/DISTURBANCE

Approximately two-thirds of children with ASD have chronic insomnia [96]. Sleep disturbances can contribute to the psychosocial burden of ASD and exacerbate symptoms such as inattention or irritability [97]. Anxiety and sensory over-responsivity alone are independently associated with a variety of sleep problems (e.g., bedtime resistance, sleep-onset delay, sleep anxiety, night waking), making children with ASD and one or both of these co-occurring conditions particularly predisposed to sleep disturbances [98]. Children's sleep habits and the sensory-processing patterns of avoidance, sensitivity, seeking, and registration were assessed in a cross-sectional study of 231 primary school students 7 to 12 years of age [99]. Each of the sensory-processing patterns was found to have a negative relationship with sleep habits, with a significant difference between children who had more challenges with sleep maintenance compared with those with normal sleep patterns [99].

ADHD

Approximately one-half of children and adolescents with ASD also may fulfill the diagnostic criteria for ADHD [87]. This co-occurrence presents a greater deficit in inhibitory control, attention, and working memory. In social cognition, the clinical features of ADHD increase the difficulties in cases of ASD [100; 101].

ANXIETY DISORDERS

An estimated 40% to 66% of school-aged children and adults with ASD are reported to also have an anxiety disorder [102; 103]. This includes separation anxiety disorder, selective mutism, specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder, and unspecified anxiety disorder. Symptoms may be present in early childhood and manifest in behaviors such as over-reactivity. Genetic factors and/or altered neurophysiologic responses to stress may predispose some to this comorbidity [87].

MOOD DISORDERS

Depressive disorders are more common among children and adults with ASD than in the general population, with reported rates ranging from 12% to 33% [102; 104]. The coexistence of a mood disorder with ASD may again be attributed to genetic factors and/or an altered neurophysiologic stress response. Chronic stress and difficulty understanding social situations may also be contributing factors to this comorbidity [87].

GASTROINTESTINAL ISSUES

Gastrointestinal issues are common in patients with ASD and may be related to problem behaviors, sensory over-responsivity, dysregulated sleep, anxiety, and irritability [82; 105; 106; 107]. Children with autism have been found to be twice as likely as children with a learning disability or other developmental delay to have frequent diarrhea and/or colitis during the past year and also were seven times more likely to have experienced these gastrointestinal problems than typical controls [108].

TREATMENT

The goals of treatment for children with ASD are to minimize core deficits; maximize functional independence; and eliminate, minimize, or prevent problem behaviors that may be interfering with the child's functional skills [10]. Intensive, individualized interventions are the most effective treatments for ASD. Early identification increases the likelihood of a favorable outcome; therefore, patients should be referred for specialized diagnostic and therapeutic interventions as soon as signs or symptoms of ASD appear [109; 110].

The intervention chosen will vary according to the child's age, strengths, and weaknesses. Other factors affecting the intervention chosen include its type and intensity, setting and/or mode of delivery (e.g., school or home, professional or trained parent), and specific target(s) of the intervention [111; 112]. It is important for clinicians to have an understanding of available interventions and of the evidence base so that they can effectively communicate with families, educators, therapists, and other service providers about the rationale for treatment recommendations.

EVIDENCE-BASED RECOMMENDATIONS

Legal mandates in education law in the United States, which include the Individuals with Disabilities Education Improvement Act of 2004 (IDEA), the No Child Left Behind Act of 2001, and its successor, the Every Student Succeeds Act of 2015, require the use of practices that are evidence-based or supported by scientifically based research [10]. The National Autism Center initiated the National Standards Project (NSP), which set the goal of establishing evidence-based standards for educational and behavioral interventions for children with ASD. Phase 1 of the NSP, released in 2009, examined and quantified the level of research that supports interventions targeting core characteristics of ASD in children and young adults younger than 22 years of age. Phase 2 of the NSP, released in 2015, provided an updated systematic review of the literature on interventions for this population. Phase 3 of the project is scheduled for release in 2021. This phase will provide updated information about interventions that have been shown to be effective [113].

The increased prevalence of ASD has increased the demand for effective treatment options, and intervention science is providing evidence about which practices are effective [114]. A report published in 2013 describes two broad classes of evidence-based interventions: comprehensive treatment models (CTMs) and focused interventions [10; 114]. CTMs consist of a set of practices designed to achieve a broad learning or developmental impact on the core characteristics of ASD [114]. Examples of CTMs include Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH) and the Early Start Denver Model (ESDM) [114; 115; 116; 117]. As of 2020, an estimated 30 CTM programs are operating in the United States [114].

The TEACCH program gathers, creates, and disseminates information about community-based services, training programs, and the latest research to individuals with ASD and their families. The program also provides clinical services (e.g., referrals, diagnostic evaluations) as well as parent support groups and individual counseling for higher-functioning clients. TEACCH conducts national and international training for teachers and other professionals and conducts research on psychologic, educational, and biomedical studies related to autism [116]. Trained ESDM therapists provide in-home training for infants and toddlers that involves their parents and families, with an emphasis on boosting the child's developmental domains of social-emotional, cognitive, and language abilities [117].

Focused interventions are designed to address a single or limited range of skills (e.g., increasing social communication, learning a specific task) that may be delivered over a short period of time. Examples of focused interventions include discrete trial teaching (DTT) and prompting [10; 114]. DTT was one of the earliest forms of applied behavior analysis (ABA). DTT was an extremely structured process, undertaken as many as 40 hours per week, that broke down desired skills and behaviors into small, discrete components, rewarding successful completion, and, in some cases, punishing unwanted behavior. DTT has since evolved [118]. Prompting procedures include any help (e.g., gestures, verbal clues) given to learners that assist them in using a specific skill. Prompting procedures often are used in conjunction with other evidence-based practices, such as DTT.

CHARACTERISTICS OF EFFECTIVE INTERVENTIONS

There is considerable regional variation in the availability of interventions for the management of ASD as well as significant overlap in the methods used. According to the AAP, the common characteristics of effective and empirically supported interventions include [10]:

- Individualized skills assessment that includes measurable goals and objectives
- Instruction provided by properly trained individuals in a low student-to-teacher ratio that addresses core symptoms and the child's individualized goals, interests, and preferences
- Collaboration among multiple providers
- An environment that is structured, predictable, organized to prevent distraction, and that promotes opportunities for the child to initiate communication and interact with peers
- Functional behavioral analysis and improvement plan based on an IDEA mandate
- Child's progress is systematically monitored and instructional strategies adjusted as needed
- Family provides ongoing input and receives education and support
- Transition planning (e.g., from school to adulthood)

BEHAVIORAL INTERVENTIONS

Many evidence-based treatment models are based on principles of ABA, which applies the understanding of how behavior works to real situations, with the goal to increase behaviors that are helpful and to decrease behaviors that are harmful or that affect learning [119]. ABA programs are typically designed and supervised by professionals certified in behavior analysis. ABA may be prescribed or recommended by a physician or licensed psychologist. ABA interventions vary from highly structured adult-directed approaches (e.g., DTT) to interventions in the child's natural environment (e.g., play or daily activities) that are adjusted according to changes in the child's development [10]. The behavioral clinician works with the family to determine the most appropriate intervention for each child. A comprehensive ABA approach for younger children, known as early intensive behavioral intervention, is supported by a few randomized controlled trials; however, few of these interventions have sufficient evidence to support their use in children younger than 12 years of age or for adolescents [120].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Academy of Child and Adolescent Psychiatry, applied behavioral analysis (ABA) techniques have been repeatedly shown to have efficacy for specific problem behaviors in children with autism, and ABA has been found to be effective as applied to academic tasks, adaptive living skills, communication, social skills, and vocational skills. Because most children with autism tend to learn tasks in isolation, an explicit focus on generalization is important.

(https://www.jaacap.org/article/S0890-8567(13)00819-8/pdf. Last accessed December 18, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

NEURODIVERSITY

Critics of ABA, including adults with autism who were once treated with ABA, contend that ABA is harmful and based on the cruel premise of attempting to make people with autism "normal" [121]. Instead of ABA, critics advocate for neurodiversity, which is broadly defined as an approach to learning and disability that suggests that diverse neurologic conditions appear as a result of normal variations in the human genome; that these variations should be recognized and respected as any other human variation; and that individuals with these variations are not in need of fixing, but rather should be recognized and respected as a social category on par with gender, ethnicity, sexual orientation, or disability status [121]. Neurodiversity challenges the assumption that ASD is a disease or disorder that needs to be eradicated, prevented, treated, or cured [122]. Self-advocating individuals with autism argue that in "highly social and unpredictable environments some of their differences may manifest as disabilities, while in more autism-friendly environments the disabilities can be minimized, allowing other differences to manifest as talents" [122].

EDUCATIONAL INTERVENTIONS

Intensive, individual special education provided by an educator familiar with instructing children with ASD is central to the treatment of ASD [7]. School-aged children with ASD should be enrolled in an appropriate educational program that provides support and promotes language, academic, adaptive, and social skills development. Federal law entitles all students with disabilities to a free and appropriate public education (FAPE) and mandates that these students be placed in the least restrictive environment that allows them to progress toward achieving their goals. These goals must be developed and measured within the framework of an individualized education program (IEP), which is a blueprint for the student's school year. The IEP includes academic and behavioral goals, interventions, modifications, supports, and hands-on learning opportunities that help the

student transition from the school years to adulthood. Parents, teachers, and other individuals who work with the student with autism all participate in developing the IEP [123].

Some students with ASD are educated in inclusive classrooms with supports; others benefit from a disorder-specific approach [114]. Classroom-based models include TEACCH and the Learning Experiences and Alternative Programs for Preschoolers and Their Parents (LEAP). LEAP blends the principles of ABA with special and general education teaching techniques to improve social interaction. One randomized controlled trial found that LEAP was associated with improvement in socialization, cognition, language, and challenging behavior. The LEAP model also was found to be superior to a treatment-as-usual method [124; 125; 126]. TEACCH was associated with more reported improvement in ASD severity for students who had greater cognitive delays. A comparison of the LEAP and TEACCH models found that their common features may be responsible for the improvements seen in all students [124].

Barriers to the child with ASD receiving appropriate educational interventions include regional variation in availability and types of therapy; long wait times for service; less-than-desired intensity of the program (e.g., may not include all components the family desires); and lack of insurance coverage [10]. In some instances, pediatricians and parents may require legal assistance to influence a local board of education to provide appropriate funding for children with ASD [7].

SPEECH-LANGUAGE INTERVENTIONS

Delays in speech onset may be complicated by general developmental delays or by coexisting speech disorders. Up to 30% of children with ASD never acquire verbal speech [127]. Speech-language therapy is the most commonly identified intervention provided for children with ASD [10]. Strategies used include reinforcement of speech sounds and communicative acts, imitation of the child's sounds, and exaggerated imitation and slowed tempo. Augmentative and alternative communication (AAC) is used when there is a deficit in spontaneous speech and includes strategies such as the Picture Exchange Communication System (PECS) and speech-generating devices [128; 129]. AAC methods teach the individual to communicate independently [10].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Scottish Intercollegiate Guidelines Network, interventions to support communicative understanding and expression in individuals with autism (e.g., the Picture Exchange Communication System) should be considered.

(https://www.sign.ac.uk/assets/sign145.pdf. Last accessed December 18, 2020.)

Strength of Recommendation: Strong

PECS was developed in 1985 and first implemented with preschool students diagnosed with autism. The primary goal of PECS is to teach functional communication. It consists of six phases and begins by teaching the individual with autism to communicate with another person by giving that person a picture of a desired item in exchange for the item. It starts with the exchange of simple icons but quickly builds to sentence structure where the child is taught to comment in response to questions [130]. Speech-generating devices and programs that use AAC on digital tablets are increasingly in use. The devices provide acoustic feedback to the child and are relatively inexpensive and portable [10].

CONSIDERATIONS FOR MEDICATION USE IN ASD
Obtain an accurate diagnosis of coexisting psychiatric conditions to guide therapy.
Use medication to manage coexisting behavioral health disorders (e.g., ADHD) and associated problem behaviors/ symptoms that cause significant impairment and distress (e.g., aggression, sleep disturbance, anxiety, inattention).
Consider medication use only after: • Accounting for when behavior began and what exacerbates it. • Obtaining functional behavioral assessment (i.e., determining if behavior is a communication of distress or a refusal). • Referral to behavior therapist has been considered. • Obtaining thorough history/physical exam. • Assessing and intervening as needed for treatable medical conditions/behavioral factors when intervention does not address symptoms of concern.
Source: [10] — *Table 6*

PHARMACOTHERAPY

Data from Medicaid and commercial insurers indicate that 56% to 65% of patients with ASD are prescribed psychotropic medications [131; 132; 133]. One or more medications are prescribed for 1% of children 3 years of age and younger; 10% of children 3 to 5 years of age; 38% to 46% of children 6 to 11 years of age; and 64% to 67% of adolescents 12 to 17 years of age [134; 135]. Increased use of medications is attributed to a lower level of cognitive skills and/or intellectual disability, disruptive behavior, or a co-existing diagnosis. A better understanding of the neurobiology of ASD will allow for identification of targeted interventions to better manage co-occurring symptoms and/or address core deficits [10]. As of yet, there is no drug that clearly leads to improvements in the basic symptoms of autism. Considerations for medication use in treatment of ASD are summarized in ***Table 6*** [10].

First Generation (Typical) Antipsychotics

Antipsychotics such as haloperidol, chlorpromazine, and thioridazine are frequently used in the treatment of adults with psychiatric disorders. They also are sometimes used to provide temporary relief from agitation, aggression, insomnia, stereotypies (i.e., repetitive behaviors), or other behavioral symptoms associated with ASD [136]. Antipsychotics also are used to help correct maladaptive behavior or as a temporary adjunct to other forms of treatment [13]. Unwanted side effects include dystonia, akinesia, akathisia, cognitive slowing, weight gain, and rarely irreversible neurologic problems, especially if used over a long period of time. Many of these side effects are reversed when the drug is stopped [2; 136; 137; 138].

Second Generation (Atypical) Antipsychotics

The atypical antipsychotic risperidone has been approved since 1993 for the short-term treatment of adults with schizophrenia and since 2003 for the short-term treatment of adults with acute manic or mixed episodes associated with extreme mood swings. In 2006, the U.S. Food and Drug Administration (FDA) approved the agent for the symptomatic treatment of irritability in children and adolescents with autism. The approval was the first for the use of a drug to treat behaviors associated with autism in children [139]. The effectiveness of risperidone in ameliorating irritable behavior in children with autism was established in two 8-week, placebo-controlled trials in 156 patients 5 to 16 years of age. These children achieved significantly improved behavioral symptom scores compared with controls [139; 140; 141]. The most common side effects of risperidone include increased appetite, weight gain, and sedation, with weight gain being the most significant [2; 138; 140; 141].

Aripiprazole, another atypical antipsychotic, also is FDA approved for the treatment of irritability associated with autism [138; 142]. In preliminary studies, the atypical antipsychotics olanzapine and ziprasidone have been shown to have similar beneficial effects, but their use in ASD is off-label [138; 143; 144; 145; 146]. Although they are effective in controlling behavioral symptoms, olanzapine and ziprasidone are associated with significant adverse effects, including abdominal pain, seizures, and excessive weight gain (olanzapine only) [138; 142; 143].

All atypical antipsychotics are associated with a high incidence of cardiometabolic side effects, such as age-inappropriate weight gain, hypertension, lipid and glucose abnormalities, and obesity [147]. These are particularly problematic during childhood, as they are strong predictors of adult obesity, metabolic syndrome, and cardiovascular morbidity and malignancy. The risk versus benefit of antipsychotic therapy should be thoroughly assessed when considering long-term use, and the agents should initially be prescribed in low doses and titrated slowly [142].

Anticonvulsants

The rate of seizures among people with ASD in community-based populations has been reported to range from 7% to 23%, with rates as high as 46% reported in clinically ascertained samples [148]. Although anticonvulsants cannot always eliminate seizures, they may reduce the number of seizures that occur. The smallest amount of medication that is effective should be used. Anticonvulsants commonly used are carbamazepine, lamotrigine, topiramate, and valproic acid [138].

Stimulants

Stimulants such as methylphenidate are sometimes used to address symptoms of hyperactivity, impulsivity, disinhibition, and inattention; however, they may not be as effective in the presence of coexisting symptoms [10; 142; 149; 150]. Treatment with stimulants has been associated with sudden death in children and adolescents with pre-existing structural cardiac abnormalities, and sudden death, stroke, and myocardial infarction have been reported in young adults [138]. Prior to initiating treatment with a stimulant, assess the patient's medical and family history of sudden death or ventricular arrhythmia and conduct a physical exam to assess for cardiac disease [138].

Antidepressants

The use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and other antidepressants have been studied for use in children and adolescents with ASD, with mixed results, and controversy persists about whether these agents should be used in these populations. For example, a 2013 Cochrane review concluded that there is no benefit, and emerging evidence of harm, with SSRIs in the treatment of ASD [151]. One meta-review assessed the effects of antidepressants for the acute treatment of ASD and found that, compared with placebo, while selected antidepressants can be effective, statistically significant differences do not always translate into clinically significant results. Additionally, there is little information about the tolerability of antidepressants in ASD, as well as little data on suicidal ideation/behavior [152].

Other Medications

Medications that have shown some promise in improving the core symptoms of ASD include donepezil hydrochloride, levocarnitine (l-carnitine), and bumetanide [153; 154; 155]. Medications that have shown mixed results include amantadine and arbaclofen [156; 157].

CAM THERAPIES FOR TREATMENT OF ASD			
Treatment	**Purpose**	**Improvement(s)**	**Adverse Effects**
Melatonin	Sleep	Sleep duration, overall sleep	Minimal to none
B6/magnesium	Correct deficiency	Social interaction, communication, repetitive behavior (in some but not all randomized controlled trials)	Neuropathy, diarrhea (at doses >200–300g)
B12	Correct deficiency	Some functioning and behavior	None reported
Multivitamin/mineral	Nutritional deficit associated with ASD	Sleep, GI, functioning, hyperactivity, self-injury	None reported
Folic acid	Genetic abnormality	Receptive, expressive language	None reported
Omega-3	Correct deficiency	Stereotypy, hyperactivity, inappropriate speech	None reported
Probiotics/GI medication	Remove toxins; improve immune function	None	None reported
Iron supplements	Correct deficiency	Restless sleep	None reported
Chelation	Remove toxic heavy metals	Language, cognition, sociability	Renal/hepatic toxicity, fatigue, diarrhea
L-Carnosine	Neuroprotective	Receptive/expressive language	Hyperactivity, excitability
Ascorbic acid (90 mg/kg)	Correct redox balance	Repetitive behavior	Can interfere with B12 absorption
Cyproheptadine	High 5-HT levels	ASD symptoms	None reported
Immune therapies	Deficiencies	Some ASD symptoms	None reported
Massage	Improve attachment; decrease overarousal	ASD symptoms, sleep, social relatedness, anxiety, disruptive behavior	Not examined
Acupuncture	Unblocking energy flow	Attention, receptive language, self-care, communication	Few, mild Possible infection, bleeding
Exercise	Decrease hyperactive, repetitive behavior	Self-stimming and academic scores	Not examined
Music therapy	Improve communication, engagement	Imitating signs/words, eye-contact, turn-taking, joint attention	Not examined
Animal-assisted therapy	Improve attachment	Playful mood, focus, language use, social awareness	Not examined
Neurofeedback	EEG changes	Attention, speech/ language, sociability, sensory cognitive awareness	Not examined

Source: [161] *Table 7*

A Report on the Hormone Secretin

Secretin is a polypeptide neurotransmitter involved in digestion. As a diagnostic agent, it may be given during an endoscopy to assess digestive function [138]. Anecdotal reports of the success of secretin have prompted a growing number of parents to seek out medical professionals willing to try the hormone on their child. However, secretin has not been approved by the FDA to treat autism, nor is it recommended by the National Institutes of Health (NIH) [158]. A meta-analysis of 14 years of data reported by the Cochrane Collaboration found no evidence that intravenous secretin, either in single or multiple doses, had any effect on function, behavior, core features, or quality of life for patients with autism [159]. Researchers concluded that the hormone should not be recommended or administered as part of the treatment plan.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Surveys of parents of children with ASD indicate that up to 95% use complementary and alternative medicine (CAM) therapies for their child's general health or to improve symptoms of ASD or associated symptoms (e.g., irritability, hyperactivity, gastrointestinal problems, sleep disturbances) [160]. In the United States, most parents report concerns regarding conventional medication safety (84%) and side effects (83%) as the main reasons for choosing CAM therapies [161]. The specific CAM therapies parents use include biologically based therapies (e.g., herbs, foods, vitamins) (54%), mind-body interventions (e.g., meditation) (30%), manipulative or body-based methods (e.g., massage) (25%), energy therapies (e.g., Reiki or electromagnetic fields) (8%), and alternative medical systems, such as homeopathy (1%) [162]. CAM therapies for which some positive research evidence exists are summarized in ***Table 7*** [161].

CAM therapies that improve physiologic abnormalities, such as oxidative stress and inflammation, hold promise for improving symptoms of ASD [160; 163; 164]. However, more research is necessary.

IMPACT OF ASD ON THE FAMILY

The impact of having a child with ASD is considerable. Parents report more stress and a greater financial burden than parents who do not have a child with ASD [165; 166; 167]. Parents also may be at increased risk of depression and anxiety [165]. Government data indicate that 57.1% of parents of children with ASD either cut back or stop working; 29.9% spend 11 or more hours per week providing care; 33.5% pay more than $1,000 annually in out-of-pocket medical expenditures; 43.0% report that the child's condition causes financial problems; and 30.6% of family members avoided changing jobs in order to maintain health insurance for their child [168].

Best practices include providing families with contact information for a family support group at the time of diagnosis [10]. Peer support for families of children with ASD has been shown to lessen parental stress, decrease negative mood, and increase positive perceptions [169]. This support may be a local group that provides face-to-face interaction and community activities, or it may be an online community. One study of peer support exchanged via social media found that parents received both informational and emotional support, including discussing and addressing the challenges and difficulties of caring for and raising a child with ASD as well as receiving information about improving children's social lives and self-care routines [170].

Families who do not reach out for support at the time of diagnosis may find the support useful later when they are faced with the transitions from preschool to adolescence to adulthood [10]. National support groups (***Resources***) and local organizations also are effective in helping families obtain information and feel supported. Clinicians should familiarize themselves with these resources. Additionally, they should advocate for instructional material in English and other languages to support a culturally diverse practice [10].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because family education is such a vital aspect of the management of ASD, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for understanding. When there is an obvious disconnect in the communication process between the practitioner and patient or patient's family due to a lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients, patient's families, and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter.

PROGNOSIS

While it is difficult to project the prognosis and trajectory of development for the child with ASD, most (more than 80%) who are diagnosed with ASD after a comprehensive evaluation at 3 years of age or younger retain their diagnosis [171; 172]. If the child has average or above-average cognitive abilities, recognition and diagnosis of ASD can be more difficult.

An estimated 9% of children who are diagnosed with ASD in early childhood may not meet the diagnostic criteria for ASD by young adulthood [10]. In these instances, the child is more likely to have a history of higher cognitive skills at 2 years of age, to have participated in earlier intervention services, and to have a demonstrated decrease in repetitive behaviors over time [173]. The prognosis for children with ASD in various subgroups (e.g., girls, racial/ethnic subgroups) requires further study [10].

A change in diagnosis (e.g., from ASD to ADHD) is more likely in the child who was diagnosed with ASD before 30 months of age. An improvement in ASD severity rating is more likely to occur in children with significant increases in tested verbal IQ; however, executive function difficulties are associated with poorer adaptive outcomes, independent of the child's IQ [174; 175]. High-functioning adults with ASD report a quality of life that is associated more with the presence and support of family and community than with management of their ASD-related symptoms [10]. As discussed, researchers are increasingly recognizing how co-occurring medical conditions can help identify the phenotypic differences within populations affected by ASD, which can influence prognosis and the choice of interventions [10].

CONCLUSION

ASD is the most common neurologic disorder in the United States; however, it often goes unrecognized and is commonly underdiagnosed. Developmental screening can be done by a number of healthcare professionals, but primary care providers are uniquely positioned to identify symptoms of ASD early in childhood. Early diagnosis is critical to identifying comorbid conditions and providing timely, appropriate treatment. Intensive, individualized interventions are the most effective treatments for ASD. They should be based on the child's age, strengths, and weaknesses and should include input from the family and collaboration among the interprofessional team.

Peer support for families of children with ASD has been shown to lessen parental stress, decrease negative mood, and increase positive perceptions. Support maybe a local group, an online community, or a national support group. Clinicians should familiarize themselves with these resources and should advocate for instructional material in English and other languages to support a culturally diverse practice.

RESOURCES

Association for Behavioral Analysis International
550 West Centre Avenue
Portage, MI 49024
(269) 492-9310
https://www.abainternational.org

Association for Science in Autism Treatment
P.O. Box 1447
Hoboken, NJ 07030
https://asatonline.org

Autism National Committee (AutCom)
https://www.autcom.org

Autism Research Institute
(833) 281-7165
https://www.autism.org

Autism Society
6110 Executive Blvd, Suite 305
Rockville, MD 20852
(800) 328-8476
https://www.autism-society.org

Autism Speaks
1 East 33rd Street, 4th Floor
New York, NY 10016
(646) 385-8500
https://www.autismspeaks.org

Autism Spectrum Connections
https://www.asconnections.org

Centers for Disease Control and Prevention Learn the Signs. Act Early.
https://www.cdc.gov/ncbddd/actearly

Eunice Kennedy Shriver National Institute of Child Health and Human Development
P.O. Box 3006
Rockville, MD 20847
(800) 370-2943
https://www.nichd.nih.gov

Family Voices
https://familyvoices.org

Global Autism Project
https://www.globalautismproject.org

Indiana Institute on Disability and Community
2810 E. Discovery Parkway
Bloomington, IN 47408
(812) 855-6508
https://www.iidc.indiana.edu

Interactive Autism Network
https://iancommunity.org

Health Resources and Services Administration
https://mchb.hrsa.gov/maternal-child-health-initiatives/autism

National Center on Birth Defects and Developmental Disabilities
https://www.cdc.gov/ncbddd

National Institute of Mental Health
6001 Executive Boulevard
Bethesda, MD 20892
(866) 615-6464
https://www.nimh.nih.gov

National Institute of Neurological Disorders and Stroke
Autism Spectrum Disorder Information Page
https://www.ninds.nih.gov/Disorders/All-Disorders/Autism-Spectrum-Disorder-Information-Page

National Institute on Deafness and Other Communication Disorders
31 Center Drive, MSC 2320
Bethesda, MD 20892
(301) 827-8183
https://www.nidcd.nih.gov

Organization for Autism Research
2111 Wilson Blvd., Suite 401
Arlington, VA 22201
(866) 366-9710
https://researchautism.org

Parent to Parent USA
https://www.p2pusa.org

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