CHAPTER

44 Autism Spectrum Disorder

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DSM-5 Diagnoses
Autism Spectrum Disorder, 722

Historical Context

Over the past several decades, our conceptualization of the pervasive developmental disorders (PDDs) has continued to evolve. Writing on schizophrenia in the early twentieth century, the Swiss psychiatrist Eugen Bleuler introduced the word "autism" to describe patients' withdrawal from reality into an inner world. Leo Kanner, an Austrian-born American psychiatrist, appropriated the term to define a new syndrome he called "autistic disturbances of affective content" (Kanner, 1943). In a 1943 publication, he reported on 11 children who shared, among other features, impairments in social relatedness, abnormal communication, and a desire for sameness. According to Kanner, the presence of "extreme aloneness" from birth distinguished these patients from those with childhood schizophrenia, who had a period of typical development prior to the onset of symptoms. Despite this observation, the first and second editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) classified autism under childhood schizophrenia (American Psychiatric Association, 1952, 1968). DSM-III, published in 1980, established PDDs as a distinct diagnostic category and laid out specific criteria for "infantile autism" (American Psychiatric Association, 1980). With the release of the revised third edition (DSM-III-R), the diagnostic criteria for this disorder, renamed "Autistic Disorder," were divided into three groups: impairments in social interaction, deficits in communication, and a restricted repertoire of activities and interests (American Psychiatric Association, 1987). DSM-III and DSM-III-R also contained criteria for Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

DSM-IV/DSM-IV-TR Subtypes

Introduced in 1994, DSM-IV presented an expanded nosology, identifying five PDDs: Autistic Disorder, Asperger's Disorder, Childhood Disintegrative Disorder, Rett's Disorder, and PDD-NOS (American Psychiatric Association, 1994). This classification scheme persisted with the publication of the DSM-IV text revision (DSM-IV-TR) in 2000 (American Psychiatric Association, 2000). The diagnostic criteria for Autistic Disorder remained organized along the three domains established in DSM-III-R. In order to qualify for the diagnosis, individuals needed to demonstrate a minimum of two symptoms of impaired socialization, one symptom of communication difficulties, and one symptom of restricted and repetitive behaviors. The DSM-IV and DSM-IV-TR criteria also required the presence of deficits in social interaction, social communication or play skills by the age of three.

In 1944 the Austrian pediatrician Hans Asperger described four patients with poor socialization, problems with nonverbal communication, intense focused interests, and motor clumsiness in the setting of relatively normal language and cognitive development (Asperger, 1944). He termed this constellation of features "autistic psychopathy." Unlike Kanner's work, Asperger's observations did not reach a wider audience until almost four decades later. Referencing his paper, British psychiatrist Lorna Wing further detailed the clinical profile, which she called Asperger syndrome, in a 1981 publication (Wing, 1981). The first English translation of Asperger's seminal paper appeared in 1991 (Asperger, 1991). As codified in DSM-IV-TR, Asperger's Disorder consisted of at least two symptoms from the social domain, coupled with one or more symptoms of restricted and repetitive behaviors, in the absence of clinically significant delays in language, cognitive functioning, or self-help skills. The DSM did not specify an age-of-onset criterion. By definition, individuals with Asperger's Disorder have a more typical early development and therefore often receive the diagnosis later in childhood. Despite achieving language milestones on time, they

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can exhibit a range of communication difficulties, from decreased prosody to poor volume modulation to impairments in social pragmatics.

Rett syndrome follows a distinctive clinical course of a period of regression and subsequent recovery or stabilization (Neul et al., 2010). The Austrian pediatrician Andreas Rett first described the unique features of this disorder in 1966 (Rett, 1966). It did not gain international attention, however, until almost two decades later with a report by Swedish pediatric neurologist Bengt Hagberg and colleagues (Hagberg, 1983). After a seemingly typical prenatal, perinatal, and early development, delays become apparent around six months of age. Despite a normal head circumference at birth, the rate of head growth slows, although this is not a universal finding. In late infancy or toddlerhood, purposeful hand skills are lost, replaced by classic stereotyped movements, such as hand wringing and clapping. Affected individuals demonstrate a regression in language skills, communication deficits, social withdrawal, and cognitive impairment. Later in the course of the disease, socialization improves and many patients develop intense eye gaze. Motor dysfunction is prominent, characterized by gait dyspraxia, muscle wasting and dystonia, and progressive kyphosis or scoliosis. Other features associated with the disorder include episodes of hyperventilation and breath-holding, bruxism, and sleep irregularities (Hagberg, 2002). In addition to classic Rett syndrome, variant forms exist, defined by different constellations of symptoms and clinical courses. The diagnosis remains a clinical one based on consensus criteria, which were most recently revised in 2010 (Neul et al., 2010). Rett syndrome predominantly affects females, with an incidence of approximately 1 per 10,000 female live births (Chahrour & Zoghbi, 2007). The majority of cases have been linked to mutations in the methyl-CpG binding protein 2 (MECP2) gene on the X chromosome. However, MECP2 defects also produce an array of neuropsychiatric phenotypes other than Rett syndrome.

Childhood disintegrative disorder presents with a pattern of significant deterioration in functioning following at least two years of apparently normal development. Thomas Heller, an Austrian educator, first characterized the disorder in 1908, which he called dementia infantilis (Heller, 1908). According to DSM-IV-TR criteria, a loss of skills occurs before the age of ten in two or more of the following domains: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills (American Psychiatric Association, 2000). Following this regression, individuals manifest autistic symptomatology, including impairments in socialization and communication, as well as restricted and repetitive patterns of behavior. In comparison to patients with autism, research has suggested that those with childhood disintegrative disorder generally have more severe intellectual disability (ID) and poorer outcomes (Rosman & Bergia, 2013). Extensive medical evaluations often do not yield an organic etiology. A rare condition, childhood disintegrative disorder has an estimated prevalence of 2.0 per 100,000 (Fombonne, 2009) and more frequently affects males.

DSM-IV-TR defined PDD-NOS as significant social deficits accompanied by either impaired communication or restricted behaviors and interests. Individuals could not have qualified for a diagnosis of one of the other PDDs, schizophrenia, or schizotypal or avoidant personality disorders. In the absence of other explicit diagnostic criteria, PDD-NOS captured a broad range of phenotypes, including "late age at onset, atypical symptomatology, or subthreshold symptomatology" (American Psychiatric Association, 2000). For instance, a child with ID and marked impairments in social communication, but no history of repetitive behaviors, could meet criteria for PDD-NOS. An individual presenting with milder social difficulties, associated with intact cognitive functioning, stereotyped interests, and a history of early language delay, could receive this diagnosis as well.

Since the introduction of the PDD subtypes, debate has ensued over their reliability and validity. Studies have highlighted decreased stability of PDD-NOS and Asperger's Disorder diagnoses, compared with Autistic Disorder, over time (Daniels et al., 2011; Rondeau, 2011; Woolfenden, 2012). Intra- and interrater variability has contributed to shifting diagnostic assignments. Across sites, interpretation of DSM-IV-TR criteria varied among expert clinicians, highlighting the lack of consistency in diagnostic labeling (Lord et al., 2012b). Given the challenges of reliably differentiating Asperger's Disorder from high-functioning autism, the boundary between these conditions has received particular focus. In general, the research has not supported qualitative distinctions between these disorders on a range of measures, including demographic characteristics, neuropsychological profiles, biological factors, clinical outcomes, patterns of comorbidity, and family history (Macintosh & Dissanayake, 2004; Witwer & Lecavalier, 2008; Via et al., 2011). These findings have bolstered arguments for a dimensional rather than categorical approach to the PDDs, prompting the reconfigured classification scheme in DSM-5.

Diagnosis

Diagnostic Features

Released in 2013, DSM-5 establishes a single Autism Spectrum Disorder (ASD) diagnosis, which replaces the PDD subtypes noted above. The diagnostic criteria include persistent deficits in social communication and social interaction evident in multiple contexts; restricted, repetitive patterns of behaviors, interests, or activities; the presence of symptoms in early childhood; and impairment in social, occupational, or other domains of functioning (American Psychiatric Association, 2013). Reflecting their overlapping symptoms, the DSM-IV-TR domains of social interaction and communication have been combined. Furthermore, the subcriterion of language delay has been eliminated from the definition, given the lack of specificity of this finding for ASD. The DSM-5 diagnosis requires the presence of past or current deficits in social–emotional reciprocity, nonverbal communicative behaviors for social interaction, and the development of relationships. Individuals must also exhibit at least two of four symptoms from the domain of restricted behavior, interests, and activities. These include stereotyped or repetitive movements, use of objects, or patterns of speech; insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior; fixated interests of abnormal intensity or focus; and hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment. Relaxing the DSM-IV-TR requirement for onset by

age three, DSM-5 states that symptoms, while present in early childhood, may not become fully apparent until social demands increase or, conversely, may be mitigated later in life by compensatory strategies. DSM-5 distinguishes the profile of symptoms in ASD from those seen in ID or global developmental delay. In individuals with these latter conditions, their functioning in social communication and social interaction corresponds to their overall developmental level. Table 44–1 provides an overview of changes in diagnostic criteria between DSM-IV-TR and DSM-5 for Autism Spectrum Disorder.

Since Kanner's initial description, deficits in socialization and communication have remained fundamental to our conceptualization of the disorder. Prospective studies suggest that the developmental trajectories of children with ASD deviate from those of typically developing children after six months of age (Ozonoff et al., 2010; Landa et al., 2013). Behavioral features manifesting in the first year of life include decreased eye contact, social interest, social smiling, displays of positive affect, and orienting to name (Zwaigenbaum et al., 2005). Children with ASD exhibit limited joint attention skills, the nonverbal behaviors (e.g., showing, pointing, gazing) used to share a point of reference with another person. Impairments in the use of nonverbal behaviors often persist, from reduced eye contact to a limited range of facial expressions and gestures. Difficulties with social and emotional reciprocity are prominent. Individuals with ASD may show disinterest in social interactions, engaging in solitary activities and failing to share their interests and emotions. Others may initiate or respond to social overtures, but navigate these interactions unskillfully. Individuals with ASD have trouble grasping social conventions, identifying and interpreting social cues, and adapting their behavior to suit different contexts. For instance, an individual might speak at length about a topic of interest, without recognizing the listener's downcast gaze and yawns as signs of boredom. The development of relationships, particularly those with peers, remains significantly impaired.

Individuals with ASD present with a range of communication problems over the lifespan. During early childhood, language delays are among the first symptoms that may prompt parent and provider concern. Parents commonly report that their children made decreased vocalizations as babies. Some individuals with ASD never develop functional speech. Those who do acquire language typically demonstrate abnormal patterns, including pronoun reversal, idiosyncratic phrases, and immediate or delayed echolalia. Echolalic content, which often consists of scripted dialogue from movies or television shows, can be used functionally in conversations as well as for noncommunicative intent. An absence of imaginative play is another common feature of the disorder. Decreased prosody and monotone pitch often characterize the speech of individuals with ASD. Even those people with relatively intact verbal abilities can struggle with higher-level skills, such as interpreting nonliteral language (e.g., humor and irony). Problems with pragmatics, the use of language in social contexts, are pervasive and include trouble with conversational give-and-take and perspective taking. Researchers have proposed that individuals with ASD possess a deficient "theory of mind," and this difficulty inferring the mental states of themselves and others to predict behavior accounts for their social and communication impairments (Baron-Cohen et al., 1985).

The ASD population exhibits a broad array of restricted and repetitive behaviors, which while not exclusive to this group, are highly prevalent. One classification system divides these into lower-level behaviors, marked by repetition of movement (e.g., stereotyped movements, repetitive manipulations of objects, repetitive self-injurious behavior), and more complex or higher-level behaviors (e.g., object attachments, insistence on sameness, and circumscribed interests) (Turner, 1999). Overall, the frequency and severity of repetitive behaviors appears to diminish over the lifespan (Esbensen et al., 2009). Motor stereotypies are seemingly purposeless repetitive movements, which include hand flapping, finger fluttering, spinning, or body rocking.

Table 44–1 Comparison of DSM-IV-TR Diagnostic Criteria for Autistic Disorder and DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

DSM-IV-TR Diagnostic Criteria	DSM-5 Diagnostic Criteria
Autistic disorder one of five PDD subtypes	Single autism spectrum disorder diagnosis
Three symptoms domains:	Two symptom domains:
1. Deficits in social interaction 2. Deficits in communication 3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities	1. Deficits in social communication and social interaction 2. Restricted, repetitive behaviors, interests, or activities
A minimum of 6 out of 12 possible symptoms	A minimum of 5 out of 7 possible symptoms
Inclusion of language delay subcriterion under domain of communication impairments	Elimination of language delay subcriterion
	Inclusion of atypical sensory experiences as a subcriterion under domain of restricted, repetitive behaviors
Onset of symptoms by age 3	Presence of symptoms in the early developmental period
Exclusion of comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD)	Removal of this restriction
	Addition of severity specifiers

These patterned movements can also involve self-injury, such as head banging or hand biting. Children with ASD commonly demonstrate repetitive manipulation of objects in their play. For instance, they will line up their toy cars or spin their wheels, without necessarily using them functionally. Individuals may demonstrate a fixation with particular objects or parts of objects, like the motors of fans. Ritualized behaviors can range from placing belongings in a particular location, to repeatedly arranging items, to food-related rituals. In contrast to the compulsions characteristic of obsessive–compulsive disorder (OCD), these behaviors appear to be pleasurable and rewarding. Individuals with ASD frequently demonstrate a restricted pattern of interests that can dominate their play, thought content, and social interactions. These preoccupations, which have a high level of intensity, can have a developmentally appropriate focus, such as a child's fascination with trains or dinosaurs. Other times they may reflect more idiosyncratic interests, for example a detailed knowledge of city subway systems. An insistence on sameness often manifests as an attachment to routines and difficulty tolerating transitions or disruptions to the schedule. Deviations from the expected course of events, such as the cancellation of a weekly activity or the need to take a different route home, can provoke great anxiety.

The domain of restricted and repetitive behaviors also encompasses sensory symptoms. Occurring across sensory modalities, these abnormalities vary in their presentation. Examples of hypo-reactivity to sensory input include a high pain threshold and decreased responsiveness to temperature. Hyper-reactivity to sensory stimuli can manifest as acute sensitivity to sounds, tastes, or odors. Tactile defensiveness, another common presentation, involves an aversion to touch, certain clothing labels and fabrics, and grooming activities such as bathing and oral care. Individuals with ASD may demonstrate unusual interest in sensory features of the environment. Sensory seeking behaviors can range from interest in spinning objects for visual input, to jumping and rocking for proprioceptive input, to mouthing objects for oral input.

To provide further descriptive information, DSM-5 contains several specifiers for an ASD diagnosis. These include "with or without accompanying intellectual impairment," "with or without accompanying language impairment," "with catatonia," "associated with a known medical or genetic condition or environmental factor," and "associated with another neurodevelopmental, mental, or behavioral disorder." Under this rubric, for instance, an individual with autistic features who meets criteria for Rett syndrome would be diagnosed with ASD associated with a known genetic condition. Incorporating a dimensional component, DSM-5 has introduced rating scales to assess the severity of current symptoms. Accompanied by descriptive text, these range from level 1, "requiring support," to level 2, "requiring substantial support," to level 3, "requiring very substantial support." Individual ratings are assigned for the domains of social communication and restricted and repetitive behaviors.

Associated Features

In addition to the core diagnostic symptoms of ASD, there are several important medical, psychiatric, behavioral, and cognitive features that are often associated with the diagnosis. Although the genetic contributions to autism remain extremely heterogeneous, recent research continues to suggest strong, though varied, genetic underpinnings (Persico & Napolioni, 2013). As such, it is imperative for clinicians to be aware of possible genetic indicators, including family history, physical dysmorphology, and concerning patterns of symptomatology that may be associated with specific genetic conditions such as fragile X syndrome (FXS). In addition, medical concerns such as mitochondrial dysfunction present a unique consideration for the ASD population. A recent meta-analysis by Rossignol and Frye concluded that mitochondrial dysfunction occurs in about 5% of children with ASD as compared to the approximately 0.01% rate seen in non-ASD children (Rossignol & Frye, 2012). Furthermore, even within the ASD population, those children with comorbid mitochondrial dysfunction showed higher rates of developmental regression, seizures, motor delay, and gastrointestinal (GI) complaints, as well as elevated lactate and pyruvate levels (Rossignol & Frye, 2012).

Some individuals with ASD also exhibit marked challenges regulating their mood and behavior. Internal drives to engage in repetitive play or actions may be viewed as a loss of behavioral control. Furthermore, individuals with ASD exhibit high levels of irritability, "temper tantrums," and low or labile mood (Simonoff et al., 2012). Some exhibit abrupt changes in mood, such as laughing for no apparent reason or becoming unusually upset by changes in routine.

Another striking, and sometimes complicating, behavioral feature seen in individuals with ASD is the presence of repetitive thoughts, speech, or action. Though repetitive behaviors are seen in other psychiatric disorders, in ASD they reflect a pattern of egosyntonic preoccupations as opposed to the markedly egodystonic obsessions and compulsions present in OCD. Individuals with autism are often quite comfortable engaging in repetitive play, motor movements, or scripted speech and can become distressed when they are prevented from doing so. In ASD, these repetitive behaviors are not aimed at preventing or reducing anxiety or distress as they might be in OCD.

The prevalence of self-injury and aggression also presents a unique concern in ASD. Self-injurious behavior (SIB) can range from relatively mild (e.g., pinching, scratching) to quite severe (e.g., head-banging, biting). SIB can be both physically dangerous and prevent an individual from participating fully in school, work, and community activities. Rates of self-injury are estimated to fall around 50%, with approximately 15% of children with ASD exhibiting more severe forms of self-harm (Baghdadli et al., 2003; Richards et al., 2012). Another study by Duerden and colleagues found similar rates of aggression, with 52.3% of individuals with ASD demonstrating aggressive behaviors (Duerden et al., 2012). Factors such as severity of ASD symptomatology and lower adaptive living skills are thought to contribute to an individual's SIB. Duerden and colleagues explored several other factors that influence self-injury and found that abnormal sensory processing was the strongest single predictor of self-injury, with need for sameness, impaired cognitive abilities, and abnormal social functioning also holding some predictive value. In addition, recent expert consensus highlights that self-injury is one of several possible behavioral indicators of abdominal pain or discomfort

in individuals with ASD (Buie et al., 2010b). Treating the underlying GI problem can help to markedly reduce or eliminate high rates of self-injury (Christensen et al., 2009). Other aggressive behaviors are equally concerning. Similar to rates of self-injury, aggression occurs in approximately 53% of children and adolescents with ASD, occurring more frequently in young children (Mazurek et al., 2013). Mazurek and colleagues found that aggression was significantly associated with clinical features such as self-injury, sleep problems, sensory problems, GI problems, communication, and social functioning (Mazurek et al., 2013). Kanne and Mazurek (2011) found that 68% of individuals with ASD exhibit aggression directed towards a caregiver, with slightly less (49%) exhibiting aggression toward a noncaregiver. Although there is some disagreement about the impact of ASD symptom severity and cognitive function on rates of aggression and self-injury, researchers agree that problems with communication are critical (Kanne & Mazurek, 2011; Duerden et al., 2012). Although aggressive behaviors are often directed toward other people, it is important to remember that individuals with ASD do not often hold specific malicious intent. Rather, aggression often stems from frustration, inability to communicate effectively with others, and limited social pragmatic problem-solving skills.

Finally, although there is limited data to support a single, distinct cognitive profile in ASD, several patterns have emerged. Individuals with ASD often struggle to process perceptual relationships, resulting in a reduced contextual understanding of their experiences (Brosnan & Scott, 2004). Many have theorized that individuals with autism demonstrate weak central coherence, resulting in limited ability to understand context or to "see the big picture" (Happe et al., 2001). Some individuals seem to demonstrate an information processing bias – focusing on "local" information as opposed to "global" information. Bolte and colleagues found that individuals with high-functioning autism showed decreased gestalt perception, which was associated with a local processing bias (Bolte et al., 2007). Formal neurocognitive testing tends to reflect patterns of relatively stronger rote learning and memory, factual knowledge, and visual-spatial problem-solving, as opposed to abstract reasoning, concept formation, and tasks involving social pragmatic knowledge, processing speed, or concentration. Although some research supports the notion of evenly developed verbal and nonverbal reasoning skill in ASD (de Bruin et al., 2006), some individuals with ASD do present with a variable neurocognitive profile similar to that seen in nonverbal learning disabilities (Stein et al., 2004). In addition, many individuals with ASD exhibit deficits in executive functioning skills, particularly the ability to modulate their attention, inhibit prepotent responses, and "multitask." Finally, intellectual disabilities are estimated to occur in more than half of all individuals with ASD (Fombonne, 2005b; Charman et al., 2011), with only a small subset of individuals with ASD displaying savant-like skills or narrow abilities that greatly exceed expectations. Intelligence quotient (IQ) scores provide one useful indicator of outcomes in ASD (Klin et al., 2005).

Assessment Issues

The assessment process for ASD varies, to some extent, depending on the age of the individual being evaluated and the local professional resources available. However, most agree that a "gold standard" diagnostic assessment should include information from many sources, including a clinical interview, direct observation, historical data, and often standardized neurocognitive or developmental testing. Many experts utilize a multidisciplinary team approach to evaluations, allowing for comprehensive assessment of an individual's complex presentation. Assessment is often further complicated by concurrent language or cognitive challenges that may make it difficult for an individual to report his or her own history or current symptoms. For these patients it is especially important to gather data from a reliable parent or caretaker.

The clinical interview should focus on gathering a complete medical and developmental history, as well as assessing the individual's capacity for social–emotional reciprocity, current relationships, past and present play and leisure skills, general interests, and response to specific sensory stimuli (i.e., sound, touch, texture). Although the relaxed DSM-5 requirement for age of onset allows for later diagnosis, it remains imperative to thoroughly assess an individual's early social development, including interests and interactions with others, eye contact, response to efforts to gain one's attention, repetitive or unusual play behaviors, and the emergence or delay in communication skills. Keen observation of a patient's behavior and social pragmatics can also be quite informative. For example, an individual with ASD may have difficulty making/maintaining eye contact or using other nonverbal behaviors to modulate social interactions. Immediately upon entering a new and unfamiliar clinic, some individuals may exhibit subtle evidence of their diagnosis. Observing interactions with a parent, caregiver, or others in the office can be particularly telling. For example, does a child seek out interactions with other children in the waiting area? Does he explore toys in an odd or peculiar fashion? Is he able to respond appropriately to social presses such as introductions or questions?

From the perspective of a physician who may be making an initial diagnosis, the medical and family history become quite important. Comprehensive medical workup should include a complete physical and neurological examination, as well as hearing and vision screenings. If any focal findings are evident on the neurological examination, an MRI of the brain should be considered. EEG may be useful if there is suspected clinical evidence of seizure activity or developmental regression. Blood tests can be useful in ruling out FXS or abnormal lead levels, particularly if other signs of exposure are evident. Additional workup may be indicated prior to initiating specific drug treatment if there is concern for potential negative hepatic or cardiac effects (McDougle & Posey, 2010).

Because it can be difficult and time consuming to gather comprehensive data of a patient's presentation across environments, symptom rating scales are often helpful in gathering information across a variety of core features of ASD (Table 44–2). Many rating scales have corresponding teacher forms that can be helpful in gathering information about an individual's symptoms across environments. In addition, many rating scales can provide an indication of symptom severity and may be useful in measuring change over time.

Table 44–2 Symptom Rating Scales in ASD

Australian Scale for Asperger's Syndrome (ASAS)
Autism Diagnostic Interview – Revised (ADI-R)
Gilliam Asperger's Disorder Scale (GADS)
Gilliam Autism Rating Scale, 2nd edition (GARS-2)
Childhood Autism Rating Scale (CARS)
Childhood Autism Spectrum Test (CAST)
Social Responsiveness Scale, 2nd edition (SRS-2)
Aberrant Behavior Checklist (ABC)
Repetitive Behavior Scale (RBS)

Although formal psychological or developmental assessment may not always be necessary for confirming a diagnosis of ASD, several very well researched tools have been developed to aid in the diagnostic classification of individuals with ASD. First, the Autism Diagnostic Interview – Revised (ADI-R) is a semi-structured caregiver interview designed to aid in the diagnosis and classification of children, adolescents, and adults for whom an ASD diagnosis is in question. (Rutter et al., 1994). The individual for whom a diagnosis is being considered must have a mental age of 2 years or above, and the respondent must be a parent or caregiver familiar with the individual's early years. The ADI-R takes anywhere from 1½ to 2½ hours to administer and score. It yields symptom information across three domains: language/communication; reciprocal social interaction; and restricted, repetitive, and stereotyped behaviors and interests. In addition to the ADI-R, the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) is a semi-structured observation tool also used to aid in the diagnosis and classification of ASD (Lord et al., 2012a). Using a series of "presses" or opportunities for an individual to demonstrate social competence, the ADOS-2 allows for direct observation of many of the core features of ASD. Specific forms of the instrument are available for toddlers, as well as children, adolescents, and adults with a variety of language levels. It takes approximately 40–60 minutes to administer with additional time required for scoring. The ADOS-2 yields information about an individual's social communication and restricted/repetitive behaviors. The instrument provides cutoff scores for "autism" and "autism spectrum," as well as comparison scores that indicate the level of ASD symptomatology compared to others with ASD who are the same age and have similar language skills. Both the ADI-R and ADOS-2 have a large base of empirical evidence supporting their utility, and both demonstrate high levels of diagnostic sensitivity and specificity (Falkmer et al., 2013).

Beyond these formal diagnostic measures, neurocognitive and developmental testing may also be helpful in determining an individual's underlying skills. This may include a formal cognitive or IQ assessment, neuropsychological testing, or adaptive skills rating scales such as the Vineland Adaptive Behavior Scales, 2nd edition (Sparrow et al., 2005). Understanding an individual's specific strengths and challenges can be instrumental in identifying the appropriate level of severity of ASD diagnosis and in establishing an appropriate treatment plan. For example, an individual with intact cognitive and language skills who struggles with higher-order social pragmatics may benefit from very different interventions than a substantially delayed young child who has not yet developed spoken communication or appropriate play skills. Furthermore, given the severe language impairments of many individuals with ASD, it is important to identify any nonverbal strengths that may aid the individual in developing compensatory strategies (e.g., learning to use a augmentative communication device).

Epidemiology

Analyzing 27 studies published between 1999 and 2010 and spanning 8 countries, researchers established 1 in 143 individuals as the best current estimate of the prevalence of ASD (Campbell, 2011). According to the Centers for Disease Control and Prevention (CDC), an estimated 1 in 88 children aged 8 had an ASD in 2008, reflecting a 72% increase from 2002 (Baio, 2012). A more recent study, looking at a nationally representative sample of children ages 6 through 17, determined a prevalence estimate of 1 in 50, based on parent report (Blumberg, 2013). The rising ASD rates have attracted the attention of the public and the scientific community. Commentary has focused on whether they signify a true increase in incidence or improved ascertainment, given the expanded diagnostic framework, greater access to services, and heightened awareness of ASD among the lay population and professionals (Fombonne, 2009).

The literature has long supported an increased prevalence of ASDs among males. Boys have a 4.6 times greater risk of ASDs than girls (Baio, 2012), but research suggests that this sex ratio diminishes among individuals with lower levels of cognitive functioning (Volkmar et al., 1993; Fombonne, 2005a). The evidence for possible racial/ethnic and socioeconomic disparities has been more equivocal. While a 2003 study showed comparable rates of ASDs among racial groups (Yeargin-Allsopp et al., 2003), the 2008 CDC data revealed significantly higher prevalence estimates for White children compared with Black and Hispanic children (Baio, 2012). Among subjects satisfying Autism and Developmental Disabilities Monitoring (ADDM) surveillance criteria, children of Black, Hispanic, or other non-White ethnicities were less likely to have a documented ASD diagnosis (Mandell et al., 2009). Some studies have identified a positive correlation between ASD risk and higher socioeconomic status (Durkin et al., 2010), while others have had the opposite finding (Rai et al., 2012). Further research will help elucidate the complex relationship between sociodemographic characteristics and prevalence rates and whether the disparities noted above reflect underascertainment in these subgroups.

The impact of the revised DSM-5 criteria on the prevalence of ASD must still be determined. Relying on retrospective data analysis and applying DSM-5 criteria in various stages of development, preliminary reports produced inconsistent findings (Mattila et al., 2011; Frazier et al., 2012; Huerta et al., 2012; McPartland et al., 2012). In the DSM-5 field trials, the prevalence of ASD remained equivalent to that of the DSM-IV PDD subtypes at one pediatric site (Regier et al., 2013). While a second pediatric site identified fewer cases using DSM-5 criteria, the combined prevalence of ASD and Social (Pragmatic) Communication Disorder, a new diagnosis introduced in DSM-5, was comparable to that of the DSM-IV PDDs (Regier et al., 2013).

Comorbidity

In terms of medical comorbidities, research indicates that a number of specific conditions often occur with ASD. These include epilepsy, FXS, tuberous sclerosis, GI symptoms, and sleep disorders. It is estimated that 10–15% of children with ASD have comorbid epilepsy with onset occurring most frequently in infancy or adolescence (Volkmar & Nelson, 1990). Similarly, the frequency of tuberous sclerosis is much higher in ASD, with nearly 20–50% of children with tuberous sclerosis also meeting diagnostic criteria for ASD (Smalley, 1998; Rutter, 2005), and 15–25% of children with FXS also meet criteria for ASD (Bailey et al., 2001). In addition, in recent years, there has been increasing recognition of co-occurring GI symptoms among individuals with autism. Research suggests that anywhere from 7% to 24% of individuals with ASD have significant, chronic GI complaints (Molloy & Manning-Courtney, 2003; Nikolov et al., 2009; Maenner et al., 2012). Experts agree that it is imperative to effectively assess and manage these complaints, as some behavior problems seem to serve as a primary indicator of underlying medical conditions, such as GI disorders (Buie et al., 2010b). Finally, individuals with ASD experience higher rates of sleep disorders, including trouble with sleep initiation and maintenance and subtle alterations of non-REM sleep (Miano et al., 2007). Up to 53% of individuals with ASD have at least one frequent sleep problem (Krakowiak et al., 2008).

Individuals with ASD also present with a variety of psychiatric comorbidities. One of the most well documented is attention-deficit/hyperactivity disorder (ADHD). Some estimates suggest that more than half of individuals with ASD also meet criteria for an ADHD diagnosis, with 26% meeting criteria for ADHD, Combined Type and 33% meeting criteria for ADHD, Inattentive Type (Goldstein & Schwebach, 2004). Although previous versions of the DSM precluded the concurrent diagnosis of ASD and ADHD, the DSM-5 now explicitly allows for this dual-diagnosis.

Anxiety issues are also prominent in ASD, although there is some disagreement about the significance of these symptoms. Some argue that co-occurring anxiety features can be attributed to the ASD diagnosis, whereas others suggest that a separate diagnostic label may be warranted. Data from structured interview research suggests that up to 94% of children with PDD-NOS met criteria for at least one anxiety disorder (Muris et al., 1998), with more conservative estimates placing the comorbidity rates at closer to 43% (Sukhodolsky et al., 2008). Social anxiety and specific phobias tend to be most common in ASD. To date, measurement of anxiety in individuals with ASD remains limited at best. Frequent deficits in language and cognitive functioning make it difficult for individuals with ASD to convey their emotional states accurately (Grondhuis & Aman, 2012). As such, when assessing for concurrent anxiety disorders, it is important to factor in clinical observations and caregiver report.

The presence of depression and mood complaints in individuals with ASD are less prominent, but still important to consider. As with other comorbid psychiatric symptomatology, assessing the symptoms of depression in an individual with ASD can be difficult, particularly as the core features of ASD may mask many indicators of depressive. Identification of depression has traditionally relied on subjective self-reports, which may not always be feasible or reliable in those with ASD (Magnuson & Constantino, 2011). Despite the challenges in confirming a specific comorbid diagnosis, many researchers have found higher rates of depression symptomatology in individuals with ASD (Chung et al., 1990; Tantam, 1991; Abramson et al., 1992; Ghaziuddin & Greden, 1998).

Finally, a diagnosis of ASD does not preclude the development of other comorbid psychiatric conditions such as schizophrenia and bipolar disorder. A careful assessment of family history and age of comorbid symptom onset is important to consider.

Course

As a neurodevelopmental disorder, evidence of ASD must be present in early childhood, even though the extent of impairment may not be evident until social demands increase. To date, the average age of diagnosis is approximately 3 years or older (Barbaro & Dissanayake, 2009); however, increasing awareness and improved early screening continue to facilitate early diagnosis (Lord & Corsello, 2005).

Since the behavioral symptoms currently used to diagnose autism do not appear within the first year of life, the true age of onset may be even earlier than recognized. Now symptoms are usually recognized during the second year of life; however, some research suggests that very subtle evidence of a difference in social attention may be present as early as the first six months of life. By analyzing retrospective video footage, Maestro and colleagues found that children who were later diagnosed with autism were less likely than their neurotypical peers to focus on social stimuli (Maestro et al., 2002). Though these signs are rarely identified in the early months of life, most parents and caregivers become concerned about their child's development around 19 months, ultimately seeking professional advice around the time their child is 2 years old (De Giacomo & Fombonne, 1998). They often first worry about a lack of developmental progress, abnormal social–emotional interactions, or a specific medical problem.

A small subset of individuals with ASD experiences a developmental regression or loss of skills early on. Although there has been some debate regarding the phenomenon of autistic regression, these periods of regression in autism have been studied extensively. The data suggest that most regression is reported between 18 and 24 months of age (Werner & Dawson, 2005; Baird et al., 2008; Stefanatos, 2008; Pickles et al., 2009). Although actual rates of regression in ASD vary dramatically, ranging from 15% to 50%, studies suggest that children who experienced a developmental regression tend to exhibit worse outcomes in the area of language and communication, play, and cognition (Bernabei et al., 2007). Concerns about hearing loss or deafness are frequently one of the first things to be ruled out.

Because specific symptom presentation and severity vary greatly among individuals with ASD, it is not surprising that the course of ASD reflects substantial heterogeneity across the lifespan. The shift of the DSM-5 to relax the age of onset requirement calls attention to the fact that some challenges may not manifest until social demands exceed the individual's capabilities. For others, symptoms may become less prominent as an individual develops compensatory strategies later in life.

Differences in Developmental, Gender, and Cultural Presentations

As noted above, ASD occurs more commonly in males, although this ratio seems to vary by intellectual functioning. Racial/ethnic and socioeconomic disparities in prevalence may reflect factors such as level of parental education and access to high-quality medical and educational resources that skew rates of diagnosis. Because individuals with ASD, by definition, show limited social–emotional reciprocity and deficits in social communication, it is imperative to consider cultural-specific factors in diagnosis. Cultural norms vary significantly with regard to appropriate and expected social interactions and relationships. Individuals with ASD should show marked impairment in social interaction when compared to their own specific cultural context. For example, deficits in eye contact should be measured in comparison to cultural norms.

Differential Diagnosis

Certain diagnostic features of ASD, such as stereotyped movements and sensory abnormalities, can present across a range of disorders. Clinicians must therefore look at the constellation of symptoms to distinguish ASD from ID and developmental delays. In contrast to these other conditions, the degree of social impairment in ASD exceeds that expected given an individual's developmental level. Making this determination can be challenging in cases of more severe cognitive impairment.

ASD must be differentiated from other communication and anxiety disorders. Social (Pragmatic) Communication Disorder, a new diagnostic category included in DSM-5, is characterized by deficits in the verbal and nonverbal aspects of social communication. Despite overlapping symptoms with ASD, a history of restricted and repetitive behaviors, interests, or activities excludes this diagnosis. Similarly, other language disorders are not associated with a pattern of stereotyped behaviors, interests, or activities. Hearing loss should also be ruled out as a cause of communication difficulties. In selective mutism, a failure to speak can produce impairments in social interactions. These features, however, manifest in particular social contexts, as opposed to the pervasive pattern of deficits seen in ASD. The behavioral characteristics of Social Anxiety Disorder (Social Phobia), such as withdrawal and avoidance, can resemble those of ASD. As defined in DSM-5, a fear of negative evaluation drives the symptoms of Social Anxiety Disorder. Outside of these specific anxiety-provoking situations, individuals with Social Anxiety Disorder generally demonstrate appropriate social interaction skills. While research has documented comorbidity of ASD and Social Anxiety Disorder, our conceptualization of the diagnostic boundaries between these conditions needs further refinement (Tyson & Cruess, 2012; White et al., 2012).

Historically, ASD was considered a subtype of childhood schizophrenia and did not emerge as a distinct diagnostic category until the publication of DSM-III. Diagnostic confusion can still occur, as the negative symptoms seen in schizophrenia – diminished affect, avolition, anhedonia, alogia, and asociality – can converge with features of ASD. Nonetheless, the conditions follow different clinical courses. In schizophrenia, including childhood-onset schizophrenia, a period of typical development precedes the onset of symptoms. By definition, ASD symptoms are present in early childhood. Positive symptoms, such as hallucinations and delusions, are hallmarks of schizophrenia, but absent in ASD.

Personality disorders should also be considered in the differential diagnosis, particularly in the assessment of adult patients. Schizoid Personality Disorder presents with patterns of social detachment and decreased emotional expression. Schizotypal Personality Disorder comprises social and interpersonal deficits, accompanied by cognitive distortions, unusual perceptual experiences, and eccentric behavior. Both these disorders are marked by social isolation and an absence of close relationships beyond first-degree relatives. Avoidant Personality Disorder is characterized by social inhibition, feelings of inadequacy, and fear of negative evaluation by others.

Etiology and Pathophysiology

Genetic Factors

Research has begun elucidating the complex genetic underpinnings of ASD. While previous twin studies established a heritability estimate of greater than 90% (Freitag, 2007), more recent data has yielded estimates of 37% for autism and 38% for the broader ASD phenotype (Hallmayer et al., 2011). The sibling recurrence rate for ASD is calculated to be as high as 18.7% (Ozonoff et al., 2011). Highlighting the genetic heterogeneity of the disorder, multiple susceptibility pathways have been identified. A number of single gene disorders confer an increased risk of ASD, including FXS, tuberous sclerosis complex, and Rett syndrome. These explain approximately 5% of total cases (Miles, 2011). Metabolic conditions, such as mitochondrial disorders and phenylketonuria, account for another 5% of individuals with ASD (Miles, 2011). Structural chromosomal abnormalities also contribute to the pathogenesis of the disorder. Cytogenetically visible chromosomal defects occur in an estimated 5% of cases, the most common of which involve maternally derived 15q duplications (Miles, 2011). Intense interest has focused on copy number variations (CNVs), submicroscopic duplications or deletions of segments of DNA which can be inherited or arise de novo. Research has detected spontaneous variants in 7–20% of cases of idiopathic ASD (Miles, 2011). A pair of studies isolated de novo CNVs in 5.8–7.9% of children with ASD from simplex families (those with only one affected offspring) (Levy et al., 2011; Sanders et al., 2011). Individually, these variants were rare, with only mutations at the 16p11.2 locus appearing in more than 1% of cases. CNVs can have variable expressivity, presenting with a range of phenotypes (Heil & Schaaf, 2013). For instance, microduplications of 16p11.2 have been linked to ASD, schizophrenia, and bipolar disorder (McCarthy et al., 2009). In addition, CNVs can have incomplete penetrance, as not all carriers will manifest symptoms (Heil & Schaaf, 2013). Sequencing exomes (i.e., the coding regions of the genome), several recent studies have investigated the association of de novo single nucleotide variants with ASD risk in both sporadic cases (O'Roak et al., 2011, 2012; Iossifov et al., 2012; Neale et al., 2012; Sanders et al., 2012) and consanguineous and/or multiplex families (Yu et al., 2013). Overall, proposed ASD candidate genes number in the hundreds and play a role

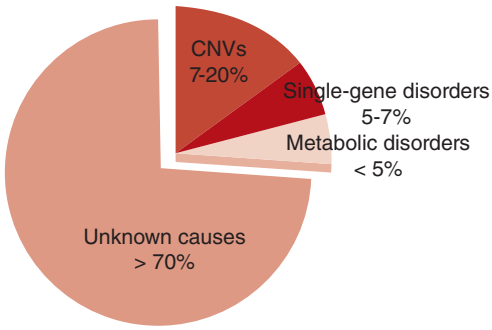

Figure 44–1 *Genetic causes of ASD. From Schaaf & Zoghbi (2011). Reproduced with permission of Elsevier.*

in multiple processes, including synaptogenesis, axon targeting, and neuron motility (Gilman et al., 2011). As seen in Figure 44–1, with our current technological capacities, a majority of affected individuals do not have an identifiable genetic etiology. Continued research will yield increasingly sophisticated diagnostic instruments, as well as expand our knowledge of the genetic mechanisms of ASD, their functional correlates, and genotype-phenotype associations.

Neurobiological Factors

Though ASD is increasingly understood as a neurobiological disorder, no single neuropathological feature or biological marker has been identified to suggest a unifying etiology for idiopathic cases. Multiple genetic loci have been implicated with each accounting for relatively few cases of ASD and likely corresponding to distinct endophenotypes of the disorder (Geschwind, 2009; Abrahams & Geschwind, 2010). Characterizing heterogeneous ASD subtypes through neuroimaging, definition of biomarkers, and connection to neuropsychological differences may ultimately yield a common neuropathological process (Geschwind, 2009).

One consistently observed finding has been normal to reduced head size at birth and a subsequent accelerated increase in head circumference in the first two years of postnatal life, reflecting brain overgrowth at an age when autistic symptoms are becoming apparent (Courchesne et al., 2001, 2003; Hazlett et al., 2005). Early overgrowth appears greatest in the amygdala, frontal, and temporal brain regions, areas involved in higher order social, emotional, language, and communicative functioning (Courchesne et al., 2007, 2011a; Geschwind, 2009). Increased brain volume appears primarily due to overgrowth of cortical and cerebellar white matter, as well as some areas of cortical gray matter, particularly in the frontal lobes (Courchesne et al., 2001, 2011b; Amaral et al., 2008). Evidence supports regional variation in the degree of neuronal overgrowth, as in the frontal lobes where overgrowth is greatest in the dorsolateral prefrontal cortex (DLPFC) and medial frontal cortex (Carper & Courchesne, 2005; Amaral et al., 2008; Courchesne et al., 2011b). The magnitude of neuronal overgrowth in the DLPFC at an early age suggests the onset of this process during prenatal life, though conclusive evidence is lacking (Courchesne et al., 2011a, b). In affected areas of the frontal cortex, cortical minicolumns, the fundamental units of informational processing, appear disrupted and are abnormal in both number and width, which may account in part for deficits in complex information processing (Casanova et al., 2002, 2006; Buxhoeveden et al., 2006; Amaral et al., 2008; Geschwind, 2009). Findings of reduced intercolumnar width in the DLPFC and Brodmann's area 9 and increased neuronal density suggest decreased dendritic arborization in the first few years of life (Casanova et al., 2006; Amaral et al., 2008). Enlargement of the amygdala has been described in young children (3–5 years old) and has been associated with more severe anxiety and impairment in social and communication skills (Juranek et al., 2006; Munson et al., 2006) To date, the cellular and molecular defects that contribute to early overgrowth in ASD are largely unknown.

Early brain overgrowth is followed by growth arrest in childhood and accelerated decline in brain size during adolescence and adulthood, perhaps indicating neuronal degeneration and highlighting the developmental nature of ASD (Bauman & Kemper, 2005; Courchesne et al., 2011a). By adulthood, the average brain of an individual with ASD is somewhat smaller than the average neurotypical brain (Courchesne et al., 2011a). Magnetic resonance imaging (MRI) and postmortem studies of adolescents and adults with ASD have revealed reduced neuron numbers in the amygdala and cortex, thinning of the corpus callosum, decreased neuron size and increased cell packing density in the cerebellum, decreased cerebellar Purkinje cells, decreased dendritic arborization, increased cerebrospinal fluid (CSF), and evidence of neuroinflammatory processes (Bauman & Kemper, 2005; Schumann & Amaral, 2006; Amaral et al., 2008; Courchesne et al., 2011a). Cortical thinning has been documented in frontal, parietal, and temporal regions containing the mirror neuron system, which some have hypothesized is critical in the expression of ASD (Hadjikhani et al., 2006). Others theorize that brain overgrowth early in development may be due to excess numbers of excitatory pyramidal neurons, triggering a compensatory proapoptotic response that accounts for growth arrest and possible neuronal degeneration in the mature brain (Courchesne et al., 2007). Developmental differences in brain growth and function in ASD complicate the study of brain-gene mapping, as pathological differences observed in adult subjects may not reflect the original causative processes (Courchesne et al., 2011a). In this regard, neurodevelopmental studies of very young children with ASD, including postmortem and functional imaging studies, are particularly important in determining the neurobiological underpinnings of the disorder.

Diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) studies have elucidated differences in structural connectivity between brain regions and connections between brain networks, respectively (Abrahams & Geschwind, 2010). Long-range white matter tracts that connect different brain regions appear reduced in some areas in ASD, including the corpus callosum, cerebellar vermis, and frontal-temporal areas (Just et al., 2004, 2007; Courchesne et al., 2011a). Deficits in long-range connections are theorized to underlie impairment in conceptual understanding and other higher-order cognitive processes, such as language development, in ASD (Volkmar, 2007). In contrast, local connections appear overgrown, perhaps explaining some individuals' isolated areas of skill (e.g., calendar calculations) and enhanced sensory processing (Herbert et al., 2004; Courchesne et al., 2007). ASD has

thus been conceptualized as a "developmental disconnection syndrome" involving brain areas subserving language, social cognition, communication, and emotional processing (Courchesne et al., 2007; Geschwind, 2009). Differences in event-related potentials (ERPs) in individuals with ASD during auditory and face processing support the concept of altered neural circuitry (Belger et al., 2011). Functional MRI studies comparing very young neurotypical children and those with ASD during processing tasks may be helpful in further characterizing aberrant functional connections.

At the cellular level, a prominent theory proposes that ASD results from a disruption of the normal process of experience-dependent synaptic development, resulting in an imbalance between excitatory and inhibitory activity (Ebert & Greenberg, 2013). A substantial percentage of candidate genes in ASD, many of them associated with CNVs or de novo germ cell mutations, are regulated by neuronal activity and thought to be involved in molecular signaling pathways that control synapse development and function (Ebert & Greenberg, 2013). For example, ASD has been associated with rare mutations in genes encoding synaptic cell-adhesion molecules, neurexins and neuroligins, which bind together to modulate synapse formation and likely play a role in experience-dependent learning and memory (Sudhof, 2008; Krueger et al., 2012). Neuroligin mutations (e.g. *NLGN4*, *NLGN3*) associated with ASD phenotypes in mice have been noted to alter excitatory or inhibitory transmission (Tabuchi et al., 2007; Etherton et al., 2009). Genetic studies in human populations suggest that neurexin and neuroligin mutations account for a very small fraction of ASD cases (Jamain et al., 2003; Pampanos et al., 2009; Avdjieva-Tzavella et al., 2012; Liu et al., 2013). Mutations in *SHANK* genes (e.g. *SHANK1*, *SHANK2*, *SHANK3*) have also been associated with ASD phenotypes, most notably in Phelan–McDermid syndrome, a rare syndromic form of ASD caused by deletion at 22q13 that involves heterozygous loss of *SHANK3* (Jiang & Ehlers, 2013). SHANK proteins form structural scaffolding in the postsynaptic density (PSD) of excitatory glutamatergic synapses that regulates the organization of postsynaptic signaling networks and impacts the morphology and function of synapses (Ebert & Greenberg, 2013; Jiang & Ehlers, 2013). The study of other monogenic disorders associated with the ASD phenotype also supports the hypothesis that disruption of activity-dependent synaptic activity may result in the autistic phenotype (Ebert & Greenberg, 2013). FXS, the most common inheritable form of ASD, results from a CGG trinucleotide expansion in *FMR1*, leading to greatly reduced or absent production of the gene product, FMRP. FMRP normally functions to downregulate activity-dependent mRNA translation postsynaptically; FMRP reduction thereby leads to increased mRNA translation and excessive synthesis of proteins that are involved in regulation of synaptic activity. *Arc*, a known mRNA target of FMRP that promotes internalization of excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) from postsynaptic membranes, is overexpressed in FXS, leading to excessive long-term depression (LTD) thought to underlie observed cognitive deficits (Snyder et al., 2001; Nakamoto et al., 2007; Akhondzadeh et al., 2008; Berry-Kravis et al., 2011; Ebert & Greenberg, 2013). Tuberous sclerosis complex, a syndrome associated with hamartoma formation in multiple organs and high penetrance of ASD, results from mutations in *TSC1* or *TSC2*, encoding for tumor suppressor proteins that modulate protein synthesis in multiple cell types (Han & Sahin, 2011). In this loss-of-function mutation, excessive signaling through the mammalian target of rapamycin (mTOR) pathway (due to loss of inhibition) leads to abnormal protein synthesis (Han & Sahin, 2011; Ebert & Greenberg, 2013). Unlike in FXS, however, activity-dependent LTD is decreased, suggesting that activity-dependent protein synthesis is finely regulated and imbalance in either direction can lead to disruption in synaptic function and contribute to the expression of ASD phenotypes (Ebert & Greenberg, 2013). Timothy syndrome, Rett syndrome, and Angelman syndrome are caused by mutations in genes that encode components of signaling networks that control activity-dependent gene transcription in the nucleus. These transcriptional targets in turn encode proteins involved in synaptic plasticity and functioning (Ebert & Greenberg, 2013). Despite these critical findings from single-gene disorders associated with the ASD phenotype, relatively little is known about the underlying molecular pathology associated with idiopathic ASD. As more is learned about candidate ASD genes and their relationship to disrupted neural processes, common molecular pathways may begin to emerge.

Psychological Factors

Psychogenic explanations of autism dominated the mid-twentieth century, influenced by the psychoanalytic ideas prevailing at that time. In his initial description, Kanner emphasized the "inborn" nature of autistic symptoms, but commented on a lack of warmth he observed among most of his patients' parents (Kanner, 1943). The notion of "refrigerator mothers," popularized by Bruno Bettelheim, implicated pathological parenting as a causal factor in ASD (Mesibov et al., 2004). Although this claim was later discredited, it had a powerful influence on the conceptualization and treatment of autistic individuals during that era, producing deleterious outcomes for patients and their families.

Other cognitive theories, such as "theory of mind" and "weak central coherence," have gained prominence and continue to account for many of the related cognitive features in ASD. Studies have shown that high-functioning adults with ASD exhibit deficits in their ability to understand the beliefs and intentions of others, as well as the meaning of nonliteral expressions (Mathersul et al., 2013). Due to these deficits in "theory of mind," individuals with ASD often have trouble ascribing mental states, thus impairing their ability to predict and understand others' behavior. In addition, nearly 50% of adults with ASD experience an inability to identify and describe their own emotions (Hill et al., 2004). The term "alexithymia," which literally means "no words for feelings," has been coined to describe this phenomenon; however, because this phenomenon occurs in individuals with and without ASD, it should not be considered a defining feature. Recent brain imaging research has found that ASD and alexithymia are separate, but related, factors (Silani et al., 2008).

Social/Environmental Factors

Rising ASD prevalence rates have focused efforts on determining possible environmental influences. As noted above, a

recent twin study provided a revised estimate of the genetic heritability of ASD, showing that the shared environmental component accounted for 55% of the liability for autism and 58% of the liability for the broader ASD phenotype (Hallmayer et al., 2011). A number of environmental factors, with varying degrees of evidence, have been investigated. Research has implicated advanced maternal and paternal age, the effects of which may be mediated through increased genetic alterations, epigenetic dysfunction, and cumulative exposure to toxins (Hultman et al., 2011; Sandin et al., 2012). The association between maternal immigrant status and ASD has been hypothesized to act through vitamin D insufficiency or maternal stress during pregnancy (Gardener et al., 2009; Dealberto, 2011). First position in the birth order also carries an increased risk of ASD (Gardener et al., 2009). In utero exposures linked to ASD include maternal rubella infection (Chess, 1971), thalidomide (Stromland et al., 1994), valproate (Moore et al., 2000; Christensen et al., 2013), organochlorine pesticides (Roberts et al., 2007), and air pollutants (Windham et al., 2006; Volk et al., 2011, 2013). One study suggested that prenatal exposure to selective serotonin reuptake inhibitors (SSRIs), particularly in the first trimester, conferred an increased risk, although these findings await further replication (Croen et al., 2011). Both maternal bleeding and gestational diabetes have also been correlated with ASD (Gardener et al., 2009). Another area of interest has been the proposed role of immune dysfunction in the pathogenesis of ASD. Accumulating evidence supports an association between familial burden of certain autoimmune diseases and ASD (Atladottir et al., 2009; Keil et al., 2010). In addition, a recent study demonstrated higher rates of anti-brain antibodies among mothers of children with the disorder (Brimberg et al., 2013).

Research has identified multiple perinatal and neonatal risk factors, including preterm birth, abnormal fetal position, umbilical cord complications, low birth weight, small for gestational age, congenital malformation, meconium aspiration, low Apgar scores, and hyperbilirubinemia (Gardener et al., 2011; Guinchat et al., 2012). A recent study linked labor induction and augmentation with increased odds of autism (Gregory et al., 2013). Further methodologically rigorous studies will help clarify whether these relationships reflect correlation or causation, sort out confounding variables, and uncover the etiologic mechanisms involved.

A great deal of controversy has centered on a possible connection between vaccines and ASD. In 1998, Andrew Wakefield and colleagues published an influential case series implicating the measles–mumps–rubella (MMR) vaccine (Wakefield et al., 1998), which prompted widespread safety concerns. The study was later retracted by the *Lancet* journal and deemed fraudulent (Godlee et al., 2011). Despite a lack of empirical support, another popular hypothesis has focused on the mercury-containing preservative thimerosal, which now has largely been eliminated from childhood vaccines in the United States. Although research has not substantiated a link between vaccines and ASD, these theories continue to have vocal proponents.

Treatment

Treatment Goals

For individuals with ASD, the overarching goals of treatment include maximizing developmental potential to achieve the highest level of independence possible and improving quality of life. ASD is a lifelong disorder, and interventions aimed at reducing core deficits in social communication and restricted or repetitive behaviors should begin as soon as impairments are identified to improve later outcome (Reichow et al., 2012). As a definitive cure for ASD does not yet exist, educational and habilitative interventions, provided with sufficient intensity and beginning at an early age, currently offer the best hope of ameliorating core symptoms (Myers & Johnson, 2007).

Given the heterogeneity of cognitive and functional abilities within ASD, treatment goals should be tailored to the particular individual's profile. For example, a high-functioning person with ASD may be fully verbal with average or above-average intelligence and capable of attending college, living independently, and holding a job. The treatment plan and goals of this individual will be quite different from those of a person with ID, no spoken language, and difficulty performing activities of daily living such as dressing, bathing, and toileting without assistance. Despite this variability, quality of life and functional independence for most people with ASD can be optimized by designing a treatment plan to address several areas of need: language development; functional communication; social skills; adaptive living skills; play and leisure skills; academic and vocational skills; and reduction of maladaptive behaviors that cause distress or impede learning and development. Areas of individual strength (e.g., cognitive or memory skills) should be used to compensate for areas of greater difficulty, and environments need to be modified in ways that allow for optimal learning (e.g., reducing visual and auditory distractions in a classroom). Treatment should also include strategies to promote generalization of skills to real-world contexts (e.g., applying conversational skills learned in a social skills group to peer interactions on the playground).

Since treatment for the individual occurs within the context of a family, an additional goal is the support and education of parents and caregivers, many of whom will care for their affected child well into adulthood.

Somatic Treatment

The use of medication and other biological therapies in individuals with ASD may be aimed at reducing core ASD symptoms or associated interfering symptoms and behaviors. To date, no medications have been approved specifically for the treatment of ASD symptoms, although controlled trials of novel medications based on translational research that target core ASD symptoms are under way and offer promise for the future. In particular, medications that modulate glutamate transmission, including memantine and D-cycloserine, have shown some initial benefit for social and communication impairments in ASD (Posey et al., 2004b; Erickson & Chambers, 2006; Chez et al., 2007; Erickson et al., 2007). Synthetic oxytocin has also been investigated for treatment of core social deficits in a number of small samples, with encouraging results (Hollander et al., 2003, 2007; Guastella et al., 2010; Anagnostou et al., 2012; Kosaka et al., 2012). Within the current practice of mainstream allopathic medicine, psychotropic medications are primarily used to reduce associated psychiatric symptoms that can cause distress and interfere with developmental progress. When effective,

medication can reduce symptom burden to a level at which an individual can more meaningfully engage in the educational and behavioral therapies that may ultimately improve core ASD features and functional outcomes.

Typical targets of medication management include irritability (including mood lability, tantrums, SIB, and aggression); compulsions and interfering repetitive behaviors; symptoms of ADHD (hyperactivity, impulsivity, and inattention); sleep disturbance; and anxiety. As with other psychiatric disorders, medication use is generally warranted when emotional and behavioral symptoms lead to functional impairment or create a great deal of distress for the individual or caretakers. A recent survey suggested that more than half of all adolescents diagnosed with ASD take at least one psychotropic medication, and 80% of all young people with ASD diagnosed with a comorbid psychiatric disorder take one or more psychotropic medications (Coury et al., 2012). Despite widespread use, there have been relatively few well-designed, controlled trials of psychotropic medications in children and adults with ASD to guide evidence-based practice (see Table 44–3 for a review of randomized, controlled trials with 30 or more subjects). Clinicians should follow a general rule of starting with a low dose of medication and titrating slowly, as many individuals with ASD appear particularly sensitive to developing adverse effects. Medication use in this population is further complicated by deficits in language and communication that frequently limit the patient's ability to report side effects and therapeutic response. Consequently, clinicians must often rely on behavioral observations and reports from parents, teachers, and other therapists to guide the treatment. Information should be gathered regularly from caretakers in multiple settings, and behavioral data collected in specialized school or home programs can be particularly helpful in monitoring response.

Irritability

Irritability is a common target of medication management in ASD and includes mood lability, severe tantrums, aggression, and SIB. Before proceeding with a medication trial, a careful medical evaluation should be done to rule out physical discomfort as a source of agitation. Possibilities include pain related to urinary tract infection, GI pain from reflux or constipation, chronic headache, and dental pain. A functional behavioral assessment (FBA) can also be helpful in determining any functions the behavior may serve for the individual (e.g., escape from demands, access to desired objects) and factors in the individual's environment that might be inadvertently reinforcing the behavior (e.g., attention from adults when the behavior occurs). Attempts should be made to modify the environment and others' responses to the behavior prior to beginning a psychotropic medication.

Atypical antipsychotics are among the best-characterized medications for use in ASD. Risperidone and aripiprazole are currently the only medications approved by the Food and Drug Administration (FDA) for use in autism, specifically for the treatment of severe irritability. Risperidone was approved by the FDA in 2006 following two multisite, randomized, placebo-controlled trials in children and adolescents with severe behavioral disturbance (McCracken et al., 2002; Shea et al., 2004). In the first trial of 101 subjects (5–17 years old), conducted by the publicly funded Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 69% of participants in the active treatment group showed a substantial reduction in symptoms of irritability compared with 12% in the placebo arm during an 8-week active treatment phase (McCracken et al., 2002). Benefits tended to persist at 6 months with open-label treatment, and a majority (62.5%) of patients in a blinded discontinuation phase relapsed with placebo substitution. In a second trial of 79 children with PDD (5–12 years old), 54% of participants in the risperidone group had a significant positive response over 8 weeks of active treatment compared with an 18% placebo response. Additional open-label and controlled trials of risperidone in participants with ASD and severe irritability have generally reported short-term response rates in the range of 57–72% (McDougle et al., 1998; Malone et al., 2002; Troost et al., 2005; Nagaraj et al., 2006). Commonly reported side effects included sedation, increased appetite, weight gain, and elevated prolactin levels. While sedation tended to abate for most by 8 weeks of treatment (Shea et al., 2004; Aman et al., 2005), weight gain was substantial in the two largest trials, averaging 2.7 kg over 8 weeks and 5.6 kg at 6 months (a 16.7% absolute weight increase) in the RUPP study (Martin et al., 2004; Shea et al., 2004). In 2009, the FDA approved aripiprazole for the treatment of irritability in children 6–17 years old with autism based on positive results from two industry-sponsored, multisite randomized, controlled trials (Marcus et al., 2009; Owen et al., 2009). Response rates for the aripirazole-treated groups were 52.2% and 55.8% compared with placebo response rates of 34.7% and 14.2%, respectively. As with risperidone, sedation was common but tended to improve within 4 weeks (Aman et al., 2010); weight gain was also common but somewhat lower at 8 weeks (+1.3–2 kg) than observed with risperidone (Marcus et al., 2009; Owen et al., 2009). Treatment-emergent extrapyramidal symptoms (EPS) and vomiting were reported more often with aripirazole than in studies of risperidone. Aripiprazole was not associated with prolactin elevation.

Other atypical antipsychotics have not been as thoroughly investigated in ASD, with studies consisting primarily of chart reviews, case series, and open-label studies. Small studies of olanzapine have yielded mixed results and demonstrated excessive weight gain (Potenza et al., 1999; Malone et al., 2001; Kemner et al., 2002; Hollander et al., 2006; Fido & Al-Saad, 2008). Open-label studies of quetiapine have found minimal efficacy for irritability and poor tolerability (Martin et al., 1999; Findling et al., 2004). Ziprasidone may be attractive for some given its relative weight neutrality, though research in ASD is limited (McDougle et al., 2002; Goforth & Rao, 2003; Cohen et al., 2004; Duggal, 2007; Malone et al., 2007), and EKG monitoring for QTc prolongation is recommended (Blair et al., 2005). Paliperidone showed promising results (84% response rate) in an open-label trial of 25 adolescents and young adults with ASD, though findings need to be replicated in a placebo-controlled trial.

While atypical antipsychotics may be the most effective available medication for irritability, they should generally be reserved for those with the most severe symptoms given the potential side effect burden, notably weight gain. Aside from risks to general health, caregivers may find it more difficulty to safely manage aggressive behavior in a heavier child. For some severely affected individuals, reduction

Table 44–3 Randomized, Controlled Trials of Medications in ASD With Minimum Sample Size of 30 Subjects

Publication	Medication	Mean Dose	Sample Size	Age Range (Years)	Study Design	Outcomes	Areas of Improvement
McDougle et al. (1996)	Fluvoxamine	276.7 mg/d	*N* = 30	18–53	12 weeks Parallel groups	8/15 (53%) fluvoxamine responders; fluvoxamine > PBO	Repetitive thoughts/ behavior; maladaptive behavior; aggression; social relatedness (especially language usage)
McDougle et al. (1998)	Risperidone	2.9 mg/d	*N* = 31	18–43	12 weeks Parallel groups	8/14 (57%) risperidone responders; risperidone > PBO	Autistic symptoms; repetitive behaviors; anxiety; depression; aggression
King et al. (2001)	Amantadine	5 mg/kg/d	*N* = 39	5–19	4 weeks Parallel groups	Amantadine = PBO on parent-rated ABC Amantadine > PBO on clinician-rated ABC, CGI	Hyperactivity; inappropriate speech
McCracken et al. (2002)	Risperidone	1.8 mg/d	*N* = 101	5–17	8 weeks Parallel groups	34/49 (69%) risperidone responders; risperidone>PBO	Irritability; repetitive behaviors; stereotypy; hyperactivity
Shea et al. (2004)	Risperidone	1.17 mg/d	*N* = 79	5–12	8 weeks Parallel groups	25/39 (64%) risperidone responders; risperidone>PBO	Irritability; hyperactivity; inappropriate speech; social withdrawal; stereotypy
Hellings et al. (2005)	Divalproex	20 mg/kg/d	*N* = 30	6–20	8 weeks Parallel groups	Divalproex = PBO	Aggression (improved in a minority of subjects)
Hollander et al. (2005)	Fluoxetine	9.9 mg/d	*N* = 45	5–16	8 weeks Crossover	Fluoxetine > PBO (effect size 0.76)	Repetitive behaviors/ compulsions
Research Units on Pediatric Psychopharmacology Autism Network (2005)	Methylphenidate	0.125 mg/kg TID, then 0.25 mg/kg TID, then 0.5 mg/kg TID	*N* = 72	5–14	1 week Crossover	35/72 (49%) MPH responders; MPH > PBO	Hyperactivity
King et al. (2009)	Citalopram	16.5 mg/d	*N* = 149	5–17	12 weeks Parallel groups	33% citalopram responders; 34% PBO responders; citalopram = PBO	None observed
Marcus et al. (2009)	Aripiprazole	5, 10, or 15 mg/d, fixed doses	*N* = 218	6–17	8 weeks Parallel groups (PBO, fixed doses of 5, 10, and 15 mg)	Aripiprazole> PBO	Irritability; hyperactivity; stereotypy; compulsions (15 mg/d); inappropriate speech (15 mg/d)
Owen et al. (2009)	Aripiprazole	2, 5, 10, or 15 mg/d, flexibly dosed	*N* = 98	6–17	8 weeks Parallel groups	52% aripiprazole responders; aripiprazole >PBO	Irritability; hyperactivity; stereotypy; inappropriate speech
Hollander et al. (2012)	Fluoxetine	64.76 mg/d	*N* = 37	18–60	12 weeks Parallel groups	7/20 (35%) improved overall with fluoxetine; 10/20 (50%) responders for repetitive behaviors	Repetitive behaviors/ compulsions
Harfterkamp et al. (2012)	Atomoxetine	1.2 mg/kg/d	*N* = 97	6–17	8 weeks Parallel groups	Atomoxetine > PBO on ADHD-RS; atomoxetine = PBO on CGI-I	ADHD symptoms, especially hyperactivity
Hardan et al. (2012)	*N*-acetylcysteine	900 mg QD × 4 wk; 900 mg BID × 4 wk; 900 mg TID × 4 wk	*N* = 33	3–10	12 weeks Parallel groups	NAC > PBO on ABC-Irritability subscale	Irritability

ABC = Aberrant Behavior Checklist; ASD = Autism Spectrum Disorder; CGI = Clinical Global Impression; MPH = methylphenidate; NAC = *N*-acetylcysteine; PBO = placebo.

of aggressive behavior may substantially improve quality of life and allow them to remain in their homes rather than requiring placement in residential care. For less severe irritability, clinicians should consider other classes of medications with less significant side effects, such as alpha-2-agonists. In general, mood stabilizers in the class of anticonvulsants, including valproate, lamotrigine, oxcarbazepine, and topiramate, have not been extensively studied or proven efficacious for the treatment of mood lability associated with ASD (Belsito et al., 2001; Hardan et al., 2004; Canitano, 2005; Hellings et al., 2005; Mazzone & Ruta, 2006; Kapetanovic, 2007; Hollander et al., 2010; Douglas et al., 2013). Of note, *N*-acetylcystine (NAC), a modulator of glutamate transmission and antioxidant-promoting agent, was recently found to significantly improve ratings of irritability in a placebo-controlled trial of 33 children with ASD (Hardan et al., 2012)

Compulsions and Interfering Repetitive Behaviors

Rituals, repetitive behaviors, and compulsions are considered core symptoms of autism. The repetitive behaviors of those with autism and those with OCD have been shown to be quite different (McDougle et al., 1995). In both disorders, these symptoms can consume a great deal of the individual's time. Unlike in OCD, however, many individuals with ASD take some comfort in these compulsive acts and do not experience precipitating obsessive thoughts. Others with ASD may experience anxiety if the behaviors are interrupted, prevented, or otherwise unable to proceed exactly as intended. In severe cases, repetitive behaviors can themselves be a source of agitation and interfere with an individual's other activities and obligations, such as schoolwork and community outings. When repetitive behaviors impede functioning or create distress to a substantial degree, medication may be considered.

SSRIs and related serotonergic agents are often thought of first for repetitive behaviors due to their relative efficacy for compulsions in OCD [Pediatric OCD Treatment Study (POTS) Team 2004; Marazziti & Consoli, 2010]. Unfortunately, results from clinical trials of SSRIs in ASD have mostly been disappointing, particularly in children. A multisite randomized, placebo-controlled trial of citalopram in 149 children and adolescents failed to demonstrate improvement in repetitive behavior, and children in the citalopram group were more likely to experience adverse effects of hyperactivity, impulsivity, impaired concentration, worsened stereotypy, and insomnia (King et al., 2009). An open-label study of fluvoxamine in 18 children did not support efficacy for the group as a whole (Martin et al., 2003), though in a placebo-controlled trial of fluvoxamine in 30 adults, 53% of participants showed significant improvement in areas of repetitive behavior, maladaptive behavior, and irritability (McDougle et al., 1996). Fluoxetine was found to be superior to placebo for repetitive behavior and compulsions in a controlled study of 45 children with ASD and a subsequent controlled study of 37 adults with ASD (Hollander et al., 2005, 2012). The tricyclic antidepressant clomipramine, a strong inhibitor of serotonin reuptake, was superior to both placebo and desipramine in a controlled study of 24 children and adolescents with ASD (Gordon et al., 1993). However, results from subsequent open-label trials of clomipramine have been mixed, with some favorable reports in adults but mounting evidence for poor tolerability in children (McDougle et al., 1992; Brasic et al., 1994, 1997; Sanchez et al., 1996; Brodkin et al., 1997). Some serious adverse events have been reported, including seizures, QT prolongation, significant tachycardia, serotonin syndrome, and increased agitation and aggression. A recent meta-analysis of controlled trials of SRIs for repetitive behavior in ASD suggested that biased publication of positive results likely accounts for the small but significant observed effect (Carrasco et al., 2012). Alternative medications are lacking, though risperidone and aripiprazole have been found to reduce repetitive behaviors and stereotypy in ASD (McCracken et al., 2002; Shea et al., 2004; Marcus et al., 2009; Owen et al., 2009). Given their burdensome side effect profiles, atypical antipsychotics should generally be reserved for those with severe compulsions or associated irritability or agitation.

ADHD Symptoms

Inattention, hyperactivity, and impulsivity are commonly co-occurring symptoms in patients with ASD. Whether this cluster of symptoms warrants a separate ADHD diagnosis or should be considered part of the primary ASD diagnosis has been debated. Unlike DSM-IV-TR, DSM-5 permits co-occurring diagnoses of ASD and ADHD. The treatment options for patients with ASD and comorbid ADHD are similar to those used for ADHD alone and include psychostimulants, alpha-2 agonists, and atomoxetine. However, the response rates tend to be lower and the side effect burden higher in the comorbid group. A number of small placebo-controlled trials, chart reviews, and one larger placebo-controlled trial of methylphenidate in children with ASD ($N = 72$) indicate that stimulants may be effective for some, but are not as well tolerated or effective in ASD as in ADHD populations (Birmaher et al., 1988; Handen et al., 2000; Stigler et al., 2004; Research Units on Pediatric Psychopharmacology Autism Network, 2005; Ghuman et al., 2009). The largest controlled trial reported a 49% response rate in children with ASD compared with the 77% stimulant response rate reported in the Multimodal Treatment of ADHD (MTA) study of typically developing children with ADHD (Greenhill et al., 2001). The discontinuation rate due to adverse effects was relatively high in children with ASD (18%), with irritability the most commonly cited reason for stopping (Research Units on Pediatric Psychopharmacology Autism Network, 2005). Other frequently reported adverse effects in this population include decreased appetite, emotional outbursts, and difficulty falling asleep. Individuals with ASD may not be able to tolerate as high a stimulant dose as their neurotypical peers with ADHD (Research Units on Pediatric Psychopharmacology Autism Network, 2005), and children with more severe autistic symptoms appear especially vulnerable to adverse effects and poor response (Stigler et al., 2004; Research Units on Pediatric Psychopharmacology Autism Network, 2005).

Nonstimulant medications may benefit individuals with ASD who have difficulty tolerating psychostimulants. The alpha-2 receptor agonist clonidine appears helpful in reducing hyperactivity, as well as symptoms of sleep disturbance and irritability in ASD, though daytime sedation is often a major limiting factor (Fankhauser et al., 1992;

Jaselskis et al., 1992; Ming et al., 2008). Guanfacine, an alpha-2 receptor agonist with a longer half-life and less associated sedation, has demonstrated response rates in ASD similar to methylphenidate (45–49%) in small studies (Scahill et al., 2006; Handen et al., 2008). As with stimulants, higher-functioning individuals without comorbid ID appear more likely to respond positively to guanfacine (Posey et al., 2004a). Symptoms of hyperactivity and impulsivity are more likely to improve with guanfacine than symptoms of inattention. Commonly reported side effects include drowsiness, irritability, and constipation (Scahill et al., 2006; Handen et al., 2008). A multisite controlled trial of extended-release guanfacine in children and adolescents with ASD is currently under way. Atomoxetine is a selective norepinephrine reuptake inhibitor that may help decrease ADHD symptom burden, particularly hyperactivity, in children and adolescents with ASD (Jou et al., 2005; Arnold et al., 2006; Posey et al., 2006; Troost et al., 2006; Zeiner et al., 2011; Harfterkamp et al., 2012). Similar to the pattern with other ADHD medications, higher-functioning individuals appear to respond more favorably than those with severe autistic symptoms or comorbid ID (Posey et al., 2006; Charnsil, 2011). Improvements appear more modest than those observed in typically developing children with ADHD (Harfterkamp et al., 2012). Children and adolescents with ASD may be more vulnerable to known side effects of irritability, fatigue, sleep disruption, and upper GI symptoms (Arnold et al., 2006; Troost et al., 2006; Zeiner et al., 2011; Harfterkamp et al., 2012). Finally, amantadine hydrochloride is a noncompetitive NMDA antagonist that was investigated in a placebo-controlled trial for the treatment of 39 children with ASD and behavioral disturbances (King et al., 2001). While clinician ratings of hyperactivity and inappropriate speech improved significantly with amantadine, parent ratings did not differ significantly from placebo. Of note, a large placebo response rate (37%) for parent ratings of overall improvement may have contributed to the failure of amantadine (47% response rate) to separate from placebo. Mild insomnia was the most commonly reported adverse effect with amantadine.

Anxiety

Anxiety is common in individuals with ASD and frequently manifests in behavioral symptoms such as restlessness, tension, sleep difficulties, resistance to change, social anxiety, tantrums, aggression, and self-injury (Hallett et al., 2013). Though medication is commonly used to treat anxiety symptoms in ASD, there is a paucity of data to confirm efficacy or guide medication choice in this population, perhaps due to the heterogeneity in the expression of anxiety and lack of reliable outcome measures. SSRIs are often considered first, though primarily on the basis of extrapolation from the anxiety disorders literature with little direct evidence to support their utility in ASD. An open-label study of nine children with ASD suggested that low-dose sertraline may be effective for anxiety associated with transitions and "insistence on sameness" (Steingard et al., 1997). Another open-label study of buspirone in 22 children found marked improvement in anxiety and/or irritability in 9 children and moderate improvement in 7 children based on overall clinical impression (Buitelaar et al., 1998). It is conceivable that reductions in repetitive behaviors and irritability observed in some SSRI studies, particularly in adults, may be secondary to more generalized improvement in anxiety. Further investigation of somatic treatments for anxiety in ASD is clearly an area of need. Placebo-controlled trials of mirtazapine, buspirone, and fluvoxamine/sertraline for anxiety in children and adolescents with ASD are currently under way.

Sleep Disturbance

Disrupted sleep patterns are highly prevalent in individuals with ASD (as much as 50–80%), including difficulty falling asleep, mid-cycle awakenings, early morning awakenings, and overall reduced sleep duration (Malow et al., 2012a). Sleep disturbance increases parental stress and may have a detrimental effect on the affected child's behavior, including core autistic symptoms (Rossignol & Frye, 2011). Abnormally low plasma melatonin levels have been documented in patients with ASD and may account for some sleep disturbance (Rossignol & Frye, 2011), though poor sleep hygiene and medical issues such as gastroesophageal reflux, abdominal discomfort from constipation, and seizures may also interfere with sleep (Mahajan et al., 2012). Clinicians should first screen for medical and psychiatric comorbidities as well as maladaptive sleep habits that may be contributing to disrupted sleep before considering pharmacologic agents (Malow et al., 2012b). Melatonin supplementation has been shown to improve sleep latency in ASD populations in numerous open-label and controlled trials (Guenole et al., 2011; Rossignol & Frye, 2011). Additional advantages of this agent include minimal side effects, low cost, and wide availability as an over-the-counter product; it is commonly considered a first-line agent for sleep disturbance in ASD. Melatonin is most effective for difficulty falling asleep and may not improve frequent night wakenings to the same degree (Rossignol & Frye, 2011). Medications other than melatonin have not been extensively studied for insomnia associated with ASD, representing an area of great need for future research given the far-reaching effects of sleep disturbance in this population. While atypical antipsychotics with sedative properties, such as quetiapine, may also improve sleep quality (Golubchik et al., 2011), their use must be balanced with the risk of metabolic and neurological side effects. Clonidine and trazodone are useful alternatives with efficacy for insomnia in neurotypical populations, though they have not been systematically studied in ASD. The melatonin receptor agonist ramelteon was reported to improve sleep patterns in 2 youths with ASD and warrants further investigation (Stigler et al., 2006).

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) is defined as a group of diverse medical and healthcare systems, practices, and products that are not generally considered to be part of conventional medicine [National Center for Complementary and Alternative Medicine (NCCAM), 2013], including special diets, supplements, and therapies. In recent surveys, approximately 28–50% of families of children with ASD used CAM treatments at some point, with higher rates among those with GI symptoms, seizures disorders, behavior problems, and greater parental stress (Perrin et al., 2012; Valicenti-McDermott et al., 2014). Use of CAM appears more prevalent in ASD than other developmental disabilities

(Valicenti-McDermott et al., 2014). Despite high rates of use, there is minimal evidence to support the efficacy and safety of most CAM interventions in individuals with ASD (Lofthouse et al., 2012). In a comprehensive review of 19 CAM treatments (13 ingestible, 9 non-ingestible), only three treatments were recommended after considering their safety, ease of use, sensibility, and expense: melatonin, multivitamins (for those with limited diet or poor appetite), and massage therapy (Lofthouse et al., 2012). Other treatments were considered low risk and worthy of consideration for short, monitored trials if conventional treatments and recommended CAM had not helped: B6 and magnesium; multivitamin/mineral (even without poor diet), folic acid, omega-3 fatty acid supplementation, L-carnosine, probiotics and GI medication (in the context of GI symptoms), iron supplementation (in the context of low ferritin), oral chelation (for confirmed heavy metal toxicity), acupuncture, exercise, music therapy, and animal-assisted therapy. Systematic reviews by the Cochrane Database of gluten-free/casein-free diets, vitamin B6-magnesium, omega-3-fatty acids, and acupuncture highlight lack of well-designed studies and insufficient evidence to support their use in the treatment of ASD (Nye & Brice, 2005; Millward et al., 2008; Cheuk et al., 2011; James et al., 2011). Based on early anecdotal enthusiasm, intravenous secretin for core symptoms of autism has been studied in over 16 randomized controlled trials with no demonstrated efficacy for ASD symptoms and is not recommended (Williams et al., 2012). Clinicians treating individuals with ASD should inquire about use of CAM to provide guidance about the risk–benefit ratio, determine if interventions are potentially harmful, and ensure that treatments do not interact with prescribed medication.

Psychosocial Treatments

There are a number of specific psychosocial therapies available to treat ASD and the related difficulties. The field has long recognized the importance of early intensive behavioral intervention, which has been found to improve learning, communication, and social skills in young children with autism (Stevens-Long & Lovaas, 1974; Lovaas & Smith, 2003). While the specific treatments vary, there are certain features that every intensive, early intervention program should encompass. Programming should occur for a minimum of 20–25 hours per week and should be provided by highly trained therapists or teachers (e.g., Board Certified Behavior Analyst or "BCBA"), though skilled paraprofessionals can implement specific therapies with direct supervision. All interventions should be guided by specific treatment goals and objectives that focus on the core areas affected by ASD (i.e., social skills, language and communication, play skills, daily living, and motor skills). Regular monitoring is required to ensure that the treatment is being implemented appropriately and that the child is progressing (National Research Council, 2001).

Several different intervention models are commonly used as part of an early treatment plan for ASD. First, applied behavior analysis (ABA) or discrete trial training (DTT) is a form of therapy based on the principles of behavior analysis that focuses on how learning takes place. Strategies such as positive reinforcement are used to increase the frequency of desired behaviors. In DTT, complex behaviors, such as requesting, are broken down into discrete skills, which are ultimately strengthened through repetition and reinforcement. Although DTT is often completed in a highly structured format in isolation, ABA techniques are often used more broadly to promote desired behaviors. Research suggests that comprehensive, long-term behavior therapy results in a substantial, positive impact on intellectual functioning, language development, and daily living and social skills (Virues-Ortega, 2010). Dr Ivar Lovaas is considered one of the fathers of behavior modification, which is often referred to as the "Lovaas method."

Pivotal response treatment (PRT) is an offshoot of Dr Lovaas' behavior modification methods developed by Drs Robert and Lynn Koegel in the 1970s. PRT is based in the general principles of ABA, with an explicit focus on "pivotal" areas of a child's development. Rather that addressing individual behaviors, PRT focuses on other factors, such as a child's motivation, response to cues, and social interactions. By targeting these pivotal aspects of development, PRT is thought to contribute to broader improvements in functioning (Koegel et al., 2010). Just as with traditional DTT, PRT focuses on motivation and reinforcement. Natural reinforcers replace the tangible or edible reinforcers that are often used in other behavior modification programs.

DIR/Floortime® is a therapeutic framework for early intervention in ASD based in the Developmental Individual Difference Relationship (DIR)-based model that was created by child psychiatrist Dr Stanley Greenspan. Using this model, parents and therapists engage with the child at their own developmental level through play-based activities that the child enjoys. Overall, Floortime does not target single skills in isolation, but focuses on building a child's emotional development more broadly; for example, working to enhance a child's overall engagement with others (Greenspan & Wieder, 2006, 2007).

Finally, the Early Start Denver Model (ESDM) combines aspects of ABA and "relationship-based" approaches to early intervention. Developed by Drs Sally Rogers and Geraldine Dawson, the ESDM provides intensive intervention in a child's natural environment. Both parents and therapists are involved in the therapy, and it is designed for children as young as 12 months old. The ESDM pulls many core components from PRT, while also integrating a relationship-focused developmental model (Rogers & Dawson, 2010). Research has found significant reduction in ASD symptom severity after two years of treatment with the ESDM (Dawson et al., 2010).

In addition to the intensive behavioral programming that is often indicated early on, various other psychosocial treatments continue to have an important role across the lifespan. Specifically, many individuals with ASD require public school programming and special education support throughout the duration of their education. Federal law entitles a student with impairing ASD to remain in the public school program until all of their educational goals and objectives are achieved or the individual turns 22 years old. All special education services for ASD should be closely monitored and documented in the student's Individualized Education Program (IEP). A variety of services, such as speech and language therapy, occupational therapy, physical therapy, academic support, and counseling, can be incorporated as part of a student's IEP as needed.

Adjunctive therapies, such as speech and language therapy are often a critical component of treatment for ASD. Speech and language therapy can be instrumental in improving language development, communication, and social pragmatics. For young children who have not yet developed spoken language, visual communication supports such as a Picture Exchange Communication System (PECS) are often used to facilitate communication and language development. With recent advances in technology, Augmentative and Alternative Communication (AAC) strategies have garnered increasing attention. Generally, AAC refers to any support that is designed to help an individual compensate for severe expressive communication deficits. Research suggests that AAC may be able to support and strengthen more effective means of communicating for individuals with ASD (Ganz et al., 2012). In addition, pragmatic curriculums, focused on "social thinking" have proven helpful in improving the social skills of individuals with ASD. Such curriculums are aimed at building the underlying cognitive skills needed to produce an appropriate social response (Crooke et al., 2008) – for example, teaching perspective-taking skills so that one can respond appropriately to another's situation.

As individuals with ASD get older, psychosocial interventions remain of utmost importance. Community and vocational supports are often essential for a person to achieve increased independence in his or her home, community, or work environments. Even high functioning individuals with ASD often exhibit a significant gap between their cognitive potential and limited adaptive skills, highlighting the importance of specific interventions aimed at facilitating independent living and adaptive skills (Klin et al., 2007).

Combined Treatment

Treatment of the child or adult with ASD requires a comprehensive approach that addresses impairments in a variety of areas, including functional communication, language, social pragmatics, learning difficulties, deficits in self-care skills, and challenging behaviors. Academic and therapeutic programming should be tailored to an individual's unique needs, though most will benefit from a combination of speech and language therapy, occupational therapy, social skills instruction, and often special education support. Given the established efficacy of ABA-based interventions for children with ASD (Granpeesheh et al., 2009), behavioral therapy, including direct services to the child and guidance to parents, should also be part of a comprehensive treatment plan whenever possible. Many children with ASD show impairment in gross motor coordination and motor planning and can benefit from physical therapy. These various services are often implemented as part of a well-tailored school program, though additional services may be provided in the private sector and are increasingly viewed as medically necessary by insurance carriers. Families may need to enlist the support of an educational advocate or consultant to ensure that a child's school program is appropriately meeting his or her needs. For some individuals with ASD, challenging behaviors, such as severe tantrums, inattention, hyperactivity, and debilitating anxiety, can interfere with developmental progress. Reducing symptom burden with medication can lead to more meaningful participation in educational and therapeutic interventions. At the same time, behaviorally based interventions may augment the positive effects of medication and allow for lower dosing regimens (Aman et al., 2009; Arnold et al., 2012). Physicians should be aware that families of patients with ASD will often seek out CAM treatments in combination with traditional allopathic approaches, and care should be taken to avoid drug–drug interactions. Similarly, medical comorbidity is common in ASD (Bauman, 2010), and psychiatrists will likely be working as part of a multidisciplinary medical team that includes neurologists, developmental and behavioral pediatricians, gastroenterologists, and primary care physicians. Awareness of other providers' interventions is essential for optimal care and harm reduction.

Treatment Refractory Patients

Educational and behavioral interventions are considered first-line treatments for children with ASD. For patients who fail to respond as well as expected to traditional treatments, consideration should be given to additional factors that may impact response, such as cognitive disability, poorly controlled seizures, GI distress, and environmental factors (e.g., placement in a noisy, overstimulating classroom for a child with auditory hypersensitivity). For nonverbal individuals in particular, a thorough physical exam and additional medical evaluation, such as an EEG, urinalysis, dental exam, or endoscopy, might be necessary to exclude medical comorbidity as a contributing factor (Bauman, 2010). Clinicians should also ensure that treatment goals and therapeutic interventions are appropriately matched to an individual's developmental level. When cognitive and physical factors have been adequately addressed and challenging behaviors such as hyperactivity, inattention, severe tantrums, aggression, or repetitive behaviors continue to interfere with treatment for ASD, psychotropic medication may be warranted. For many target symptoms, however, medication response rates in children with ASD are lower than in neurotypical children with similar symptoms (e.g., hyperactivity in ADHD or compulsions in OCD), and some may not respond to or tolerate any medications well. Individuals with more severe ID appear particularly vulnerable to poor treatment response. As in other psychiatric disorders, combinations of medication may be tried when an individual has a partial response to monotherapy or cannot tolerate a therapeutic dose of a particular agent. Combined treatments, however, have not been systematically studied in ASD. When educational and behavioral interventions, optimal medical management, and psychopharmacological trials have been exhausted with minimal success, some children will benefit from highly structured residential school programs for the most intensive service delivery.

Special Factors Influencing Treatment

Medical comorbidity is common in individuals with ASD but may go undetected, particularly in individuals with minimal language or relative insensitivity to pain (Bauman, 2010). For this reason, evaluation of new or challenging behaviors should include a comprehensive inventory of symptoms, physical exam, and other potentially relevant studies. For those with known medical conditions, psychiatric management should be conducted in collaboration with other medical specialists. For a child with epilepsy and concomitant irritability, for example, a psychiatrist may work together with the neurologist to select an anticonvulsant that

may have mood stabilizing properties, like valproate, while remaining wary of potential cognitive and behavioral side effects of anticonvulsants in general (Depositario-Cabacar & Zelleke, 2010). The treating psychiatrist should also remain cognizant that some psychotropic medications, such as atypical antipsychotics, may lower the seizure threshold and worsen seizure control, and increased seizure activity may also contribute to behavioral deterioration. GI disorders, such as chronic abdominal pain, constipation, and gastroesophageal reflux, are also common in individuals with ASD, and the most apparent presentation of these disorders may be behavioral disturbance (Buie et al., 2010a). For children with known constipation, commonly used psychotropic medications such as guanfacine and risperidone may exacerbate this condition.

Just as psychiatric clinicians must consider medical comorbidity in treatment, clinicians should also become well versed in educational and behavioral interventions, the mainstays of treatment for ASD, to determine if therapeutic programming is appropriately addressing the patient's needs. When changes are recommended, care should be taken to advocate for the needs of the child while maintaining a good working relationship with schools and other providers. Similar challenges may be encountered as a child graduates from the school system and moves into the adult care system, potentially requiring residential care and day habilitation.

Issues in Clinician–Patient Relationship

Due to social communication and language impairments inherent in ASD, the patient is often not the primary reporter of symptoms, and clinicians must gather information from a variety of sources, including parents, residential caretakers, and teachers, in order to make informed treatment decisions. At times, this data collection may be time consuming and cumbersome, though for patients unable to self-advocate, it is of utmost importance to collect as much information as possible in order to act in their best interest. For higher-functioning individuals with some degree of language, clinicians should continue to seek out their point of view, maintain confidentiality, and obtain informed consent for treatment whenever possible. In patients without well-developed expressive language, their receptive language abilities may be much more advanced, and every effort should be made to include them in discussions. For adult patients, physicians should determine if a patient has a legal guardian for medical decision-making, and all treatment decisions should be approved by this individual. Clinicians may also be asked to provide documentation to support a caretaker's petition for guardianship. As part of this process, the psychiatrist will need to determine the individual wishes of the patient, if possible, and perform a complete assessment of functional, cognitive, and communicative abilities. Efforts should be made to preserve as much autonomy as reasonably possible when recommending guardianship responsibilities. Finally, clinicians working with patients with ASD need to remain flexible in meeting patients with special needs in non-traditional contexts, such as group homes, waiting areas, and in the company of a caretaker, though this represents a departure from traditional psychiatric encounters. Remaining sensitive to difficulty tolerating transitions and having soothing sensory objects and toys on hand can decrease anxiety and agitation around appointments.

Clinical Vignette 1

Jacob was the first child born to a 39-year-old mother and 44-year-old father at full-term by a normal spontaneous vaginal delivery following an uncomplicated pregnancy. His mother did not take any medications other than a prenatal vitamin during the pregnancy. His parents described Jacob as a quiet baby who seemed content to entertain himself, rarely crying or holding up his arms to be picked up unless very distressed. He was visually attracted to a hanging mobile in his crib and could spend "hours" watching it spin if his parents did not intervene. Jacob achieved his early gross motor milestones at the expected times, sitting independently at seven months, crawling at ten months, and taking his first steps at 13 months. His parents first became concerned about his development when he was 14 months old, as he was not babbling and did not have any early words like the other children in his mother–baby play group. His pediatrician evaluated him and reassured his parents that children develop language at different rates.

When Jacob presented to his pediatrician again at 18 months old, he still had not begun to talk, and his parents had observed other differences between their son and his peers. While other children his age were starting to play with their toys in an imaginative way, Jacob continued to mouth his toys or bang them together in a nonfunctional way. He had also developed a strong interest in spinning tops and would sometimes hold objects very close to his face, gazing at them in his peripheral vision. He was very attached to a particular shoelace that he liked to hold and shake. When he was excited, he would flap his hands. On examination, Jacob did not make eye contact and did not respond to his name being called, although he appeared anxious, crouching and covering his ears with his hands, when he heard an infant crying in the hallway. He subsequently passed a hearing test. Jacob had a neutral facial expression and rarely smiled. While he became excited when offered the examiner's measuring tape to hold, he did not reference his mother as expected to see if she shared his interest. He appeared healthy and did not have any apparent dysmorphic features, birthmarks, or distinctive skin markings. After evaluation by a developmental and behavioral pediatrician, Jacob was diagnosed with an autism spectrum disorder (ASD) and referred for Early Intervention services, including speech and language therapy, occupational therapy, and intensive Applied Behavioral Analysis (ABA) therapy at a rate of 30 hours per week.

When Jacob entered a specialized ASD preschool program through the public school system at age three years old, he still was not speaking, though he had begun to make nonspecific vocalizations and used a few nonverbal gestures to communicate, including the signs for "more," "eat," and "all done." His teachers found it difficult to obtain his attention or sustain his focus for more than a few minutes on a given task, though he responded well to concrete rewards for his efforts, such as time to play with his tops. Jacob also appeared more at ease when he was given a picture schedule to preview the day's events, but he would often flop to the floor and cry if asked to do something unfamiliar or challenging to him. While he seemed indifferent to his peers, he developed a particular attachment to his head teacher, seeking her out and holding onto her leg when upset. He was bothered by the sound of other children crying and loud, unexpected noises. He toilet trained for bladder control at age four years old and for bowel control at five years old, though he continued to have nocturnal enuresis.

At age six, Jacob entered a substantially separate kindergarten classroom in a public elementary school that was based on principles of ABA. He began to speak a few word approximations, mostly using language to initiate a request for something he wanted. His eye contact remained poor. Jacob was unable to sustain a conversation and was aloof with his peers, preferring to engage in stereotyped motor behaviors during his downtime, including spinning and shaking objects. These activities could be distracting, and he required a one-to-one aide in order to focus on a task for even a few minutes. At home, Jacob could follow one-step directions some of the time, but often got absorbed in a preferred activity along the way and did not follow through. During meals, he would wander away from the dinner table after only a few minutes, often taking more than an hour, with coaxing from his parents, to complete a meal. Jacob had rigid food preferences and a limited diet of hot dogs, chicken nuggets, French fries, pancakes, and apples. He gagged on any foods with a mushy texture. His tantrums improved substantially with age, though eliciting his cooperation could still be difficult when he had little interest in a task. Jacob continued receiving in-home behavioral therapy 8 hours per week with a focus on social communication (e.g., making eye contact, social greetings) and self-care (e.g., dressing self, washing hands). His IEP at school included speech therapy and occupational therapy twice a week, as well as participation in a weekly social skills group.

At age nine, Jacob had a trial of methylphenidate for his difficulty sustaining attention. He appeared more withdrawn and had frequent crying spells while taking it, and the medication was discontinued. Jacob was subsequently treated with guanfacine, which he tolerated better, with some modest improvement in his attention span and decrease in motor stereotypy. Overall, his parents felt that he appeared calmer and more responsive to their requests.

In middle and high school, Jacob remained in a substantially separate classroom for children on the autism spectrum. He learned to recognize a few words by sight and could write his name, though he did not read. Jacob developed a limited vocabulary of approximately 50 words, and most of his speech was limited to one- or two-word phrases. He remained interested in spinning objects, but his motor stereotypies declined significantly. Jacob's curriculum shifted from basic academic work to life skills instruction and vocational training. By the end of high school, he was able to perform most self-care activities, such as bathing and brushing his teeth, independently with some assistance for thoroughness. He enjoyed supervised jobs folding laundry at a nearby hotel and shredding paper at an office. Jacob did not develop a concept of money and could not make change. He did not independently use the stove or dishwasher to prepare meals for himself. Although he did not develop meaningful relationships with his peers, he was affectionate with his parents and seemed to enjoy their company.

When Jacob turned 18, his parents applied for and obtained legal guardianship and Supplemental Security Income benefits. After graduating from high school at age 22 with a certificate of completion, he moved into a group home for adults with developmental disabilities, attending a nearby day habilitation program five days a week. His parents established a financial trust for him in planning for their eventual demise. Jacob continued to spend weekends at home with his parents, who remained devoted to providing him with enriching experiences, including vacations and community outings.

Clinical Vignette 2

Ryan was the third child born to his 36-year-old father and 34-year-old mother, who took medication for Hashimoto thyroiditis during her pregnancy with him. He was born at full term following an uncomplicated delivery and was discharged from the hospital with his mother. As an infant, Ryan cried a lot and could only be soothed by vigorous bouncing or rocking. He had a difficult time breastfeeding and was switched to formula after a few weeks of poor weight gain. His parents recall that he was also a restless sleeper and was highly sensitive to any ambient sounds.

Ryan was somewhat delayed in meeting gross motor milestones, crawling at 12 months and walking at 18 months, and he seemed to move about in a clumsy manner. He was a precocious talker, however, speaking his first words at 11 months and conversing in full sentences by 20 months. He loved books and was particularly enamored with a collection of train photographs in the family's home. By three years old, Ryan could recite numerous facts about different train models, which never failed to impress his parents' friends. His parents, however, were exhausted by his intense interest in trains and his ability to steer any conversation back to that topic. Ryan was sensitive to minor frustrations, such as difficulty locating a preferred toy train, and would sometimes have prolonged "meltdowns" if something did not happen as he expected. He also developed a tendency to ask questions in a repetitive manner, particularly when he was anxious.

When Ryan entered preschool, his teachers expressed concern that while he was clearly bright and a delight for the adults in the classroom, he was having some difficulty relating to his peers. He gravitated toward solitary play with building blocks, and when he did try to join in his classmates' free play, he could be rigid and directive, becoming upset if other children didn't adhere to his rules for the game. He did not seem to have any true friends, though he named another boy who also liked trains as his best friend. Ryan's parents became increasingly concerned about ASD, as he had a first cousin with autism and an 8-year-old brother who had been recently diagnosed with nonverbal learning disability. While his father, a software engineer, had never been formally diagnosed with ASD, he recalled his own social difficulties as a child and an unusual ability to focus on numerical data for extensive periods of time. Ryan underwent comprehensive neuropsychological testing at age four and was diagnosed with ASD. He was found to be quite intelligent, with verbal abilities in the superior range but nonverbal scores in the average range. His tendency to get "stuck" on problems that he could not answer immediately may have contributed to underestimation of his true abilities.

Ryan excelled academically in school but had ongoing difficulty in his peer relationships. He longed for friendships, and while his mother went to great lengths to orchestrate play dates for him, his classmates tended not to accept her invitations after a few initial get-togethers. She noted that he remained domineering in his play and preferred to act out a few scripted stories from his favorite movies, which bored the other child. He also had a tendency to talk excessively about trains with no awareness that his playmate had lost interest. He was rarely invited to birthday parties. Ryan's IEP at school included a structured weekly social skills group, individual speech therapy with a focus on language pragmatics, and an informal "lunch bunch" to practice his

social skills. His parents also enrolled him in a private social pragmatics group on weekends and a summer camp for children with high-functioning ASD. Ryan developed friendships with two other boys in these groups who had similar social challenges.

As Ryan approached high school, he was subjected to verbal bullying from a few select classmates, and he became increasingly aware of his differences and ostracism from his mainstream peers. He developed symptoms of depression, including low mood, irritability, social withdrawal, and anhedonia. Ryan entered counseling, but had a difficult time connecting with his therapist, who he complained, "just sat there, waiting for me to talk." He started refusing to attend appointments. His pediatrician prescribed fluoxetine, which was modestly helpful for his depressed mood, and referred Ryan to a cognitive behavioral therapist, who proved to be a better match for him.

In high school, Ryan found that academics continued to come easily to him, though he struggled with his personal organization skills. His grades were only average due to frequently turning in assignments late or failing to complete them at all. He could be moody and argumentative with his parents, and he resisted his mother's prompts to shower, brush his teeth, and keep his room clean. At home, he preferred to spend most of his time alone in his room, playing role-playing video games online. He reported having a network of "close friends" in this online gaming community, and his text exchanges with them constituted the bulk of his social activity. He showed little interest in extracurricular activities such as sports and youth groups, and his parents eventually stopped enrolling him in them.

Ryan graduated high school at 18 with a 2.7 grade point average and enrolled in a local community college, completing 3 semesters with great difficulty. He ultimately dropped out in his 4th term due to failing grades, poor motivation, and limited organizational skills. He continued to live at home with his parents and struggled to find a job, though he was eventually hired for part-time data entry at a local business. He began dating a young woman whom he met through a favorite Web site, though they only met in person on rare occasions. Ryan's parents renovated a studio apartment over their garage for him, and he moved in and paid them a small amount of rent. He had bouts of depression and difficulty maintaining jobs throughout his adult life and described frequent feelings of loneliness. While his parents worried that the long periods of time he spent on the computer interfered with his social opportunities, he reported that he felt most comfortable with his online friends and that this was one of his few sources of pleasure.

Summary

Since Kanner's and Asperger's initial descriptions, our conceptualization of ASD has continued evolving. While research has yielded insights into the complex genetics and neurobiology of the condition, many questions remain unanswered. In particular, the biologic and phenotypic heterogeneity of the disorder have impeded efforts to identify the underlying pathophysiology. At the same time, rising prevalence rates have given these investigations added urgency. It is hoped that further scientific advances will not only expand our understanding of ASD, but will also translate into more effective therapeutic interventions and improved clinical outcomes for this population.

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