Autism has long been the paradigmatic syndrome for a group of conditions most recently classified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) under the category of Pervasive Developmental Disorders. However, more recent considerations of this group of conditions suggest that a spectrum of symptoms more accurately reflects the nature of these disorders, leading to the current concept of Autism Spectrum Disorders (ASDs).

Autism and the ASDs come from a long history of confusion and stigma. Even before the syndrome was originally named by Leo Kanner in his 1943 paper, as a condition of “autistic disturbance of affective contact,” the condition has been the focus of considerable confusion. Some of this confusion comes from the association of the term “autism” with the so-called “4 A’s” that Eugen Bleuler used to characterize schizophrenia. This was compounded by descriptions of Victor, the Wild Boy of Aveyron who, after allegedly having been reared by wolves, was brought to Paris and trained by the French psychologist Itard. And, with the advent of the psychoanalytic era of psychiatric theories, Bettelheim’s Empty Fortress and Margaret Mahler’s “normal autistic phase” of development suggested that failures in parenting caused this pervasive and persistent disorder. This early work gave rise to notions about “refrigerator” mothers as the cause of such serious psychopathology and created an enormous burden and stigma for parents seeking to understand and care for their children. Sadly, some of these biases and misconceptions persist to this day, interfering with early diagnosis and treatment as well as scientific approaches to research on autism.

Today we understand ASDs to be a group of clinical syndromes that have varying degrees of two fundamental elements: developmental delays and developmental deviations. Two-thirds of cases have evidence of atypical development before 12 months, and one-third of cases have a regression in speech and language before 18 months. Onset occurs before 30 months for all but childhood disintegrative disorder. The core syndrome includes deficits in social interactions and communication, along with presence of stereotyped behaviors, activities, and interests. The prototypic ASD is autistic disorder. The other ASDs, including Rett’s disorder, childhood disintegrative disorder, Asperger’s disorder, and pervasive developmental disorder not otherwise specified (PDD NOS), share many of the core features of autistic disorder.

Epidemiology

By the standards of childhood onset disorders, ASDs have long been thought to be relatively common; however, there have been recent concerns about recurring reports of rising ASD prevalence and the possibility of an ASD epidemic. Studies of ASD, conducted since 1985, have reported progressively higher prevalence estimates, ranging from 0.07% to 1.8% [1–7], and an even higher rate of 2.64% from the most comprehensive, total population-based survey to date [8]. Review of studies across cultures reveals similar rates of autistic disorder and consistent phenomenology, and ASDs are seen throughout all socioeconomic levels [5, 9, 10]. Autistic disorder has been reported to be four times more prevalent in males than females [9, 11], but this has been questioned by more recent work [8]. The other ASDs seem to be similar to autistic disorder with a greater ratio of affected males, except in the case of Rett’s disorder, which is diagnosed almost exclusively in females.

Historically, about one-half of children with autistic disorder are said to have an intellectual disability (ID; or mental retardation), with intelligence levels ranging from profoundly retarded to above average in autistic disorder and the other ASDs [9, 12]. A notable exception
may be childhood disintegrative disorder, in which all affected children are mentally retarded [13].

Follow-up studies of autistic disorder have suggested that, when present, ID persists from the time of diagnosis onward [14]. Intelligence quotients (IQs) tend to be stable over time and are felt to be one of the most important predictors of outcome in autism [15].

Individuals with ASD have been said to have relative strengths in visuospatial skills and rote memory skills [16]. A small number of individuals with ASD are reported to have phenomenal abilities in particular areas, such as in memory, calendar calculation, or artistic endeavors. These so-called “savant” talents are also seen in individuals with other developmental disorders [17].

As one looks closer at the issue of ASD prevalence, more recent data suggest that most of the ASD prevalence increases are attributable to a combination of factors, most likely including: greater public awareness; better case ascertainment; broadening of the ASD diagnostic construct; lower age at diagnosis; diagnostic substitution; and target study population [7]. This is best exemplified in a comprehensive, total population study that examined both the clinical samples that were the targets of previous studies as well as a general population. This landmark study by Kim et al. found an overall ASD prevalence of 2.64%. This number is striking, but even more striking was their finding that while 0.75% of the children were enrolled in special education schools, a disability registry and/or receiving psychiatric services, 2/3’s or 1.79% although clearly clinically impaired, were attending regular education schools and had no prior psychiatric/developmental evaluations or services. There were two equally important findings: the male:female ratio in the group receiving services was 5 : 1, whereas it was 2.5 : 1 in the regular education group. IQs varied as well, with a mean IQ of 75 in the special education group and of 98 in the regular education group [8]. Taken together, these data indicate that sample selection and careful measurement play a big role in determining the prevalence and clinical phenotype in groups of individuals with ASD.

What remains uncertain is if increased ASD prevalence is even partially attributable to a true increase in incidence. While more than 40 surveys have been conducted to examine ASD prevalence in North America, Europe, and Asia, only a handful of studies have examined ASD incidence, reporting incidence rates ranging from 0.4 to 33.7/10,0000 [5, 18–27]. Furthermore, methodological limitations (such as retrospective case identification from available records and inconsistent use of various diagnostic criteria) do not allow for the examination of changes in ASD incidence over time. Accurate incidence estimates, measured in a prospective study of consecutive birth cohorts using systematic and standardized assessments, are essential for determining if the increasing ASD prevalence is even partly caused by increasing ASD incidence; such an increased incidence may suggest that some environmental factor(s) and their interactions with genetic vulnerability are possible risk mechanisms for ASD.

In conclusion, ASD prevalence is definitely increasing over time but there is no evidence of a so-called epidemic. However, it is still possible that small to modest increases in incidence may be accounting for a meaningful proportion of the reported prevalence rises. More study is urgently needed to address this problem.

**Etiology and Pathophysiology**

At this time, the precise etiologies and pathogenesis of ASDs are unknown. Early biological hypotheses focused on neurotransmitter abnormalities as a cause of autistic disorder, starting with Freedman’s early observation of hyperserotonemia in many individuals with autism [28]. This has been replicated numerous times [29], proving it to be one of the most enduring biological findings in psychiatry. Hyperserotonemia is most likely due to genetic variations leading to abnormalities in the functioning of proteins involved in serotonergic regulation, such as the serotonin transporter and serotonin 5-HT2A receptor, which are expressed in both the developing brain and platelet [30, 31]. A range of 30% to 75% of autistic individuals have nonspecific neurological abnormalities including: poor coordination, hypomotoricity, choreiform movements, abnormal posture and gait, tremor, and myoclonic jerking [32]. About 25% of autistic individuals develop seizures by the end of adolescence or electroencephalographic (EEG) abnormalities [33]. This phenomenon has been highly correlated with mental retardation and may be more correlated with mental impairment than the presence of PDD or autism [33, 34]. Seizures with onset in adolescence often generalize, but are typically infrequent [35]. Though these early observations are historically relevant and give a unique insight into the neurobiology of ASDs, advances in the sensitivity of genomic and neuroimaging technologies, particularly in the past decade, have further contributed to overwhelming evidence for a strong, yet complex, neurodevelopmental disease process.

Autism spectrum disorders are arguably the most heritable psychiatric illnesses according to twin and family studies. Concordance in monozygotic twin pairs has ranged from 60% to over 90%, while dizygotic twin pairs in these studies have generally found a concordance rate similar to that found in siblings of unaffected
When considered as a spectrum disorder, twin studies suggest that at least 92% of monozygotic twin pairs are concordant for at least milder but similar deficits in the social and communication realms, compared to a 10% rate in these studies for dizygotic twin pairs [36]. Since the ASDs are often associated with mental retardation, the search for etiology has included common factors. For example, individuals with fragile X syndrome are considered to have a higher prevalence rate of autism [38]. While fragile X syndrome may account for only a small number of cases of ASDs, most children with fragile X syndrome have an ASD [39]. Other genetic disorders have been associated with ASDs, including duplications of the proximal portion of the long arm of chromosome 15 [40, 41], phenylketonuria [42], and tuberous sclerosis [43]. A significant advance occurred with the ascertainment of a genetic basis for Rett’s disorder; mutations in the gene, MECP2, encoding X-linked methyl-CpG-binding protein 2 (MeCP2) have been identified as the cause of more than 80% of classic cases of Rett’s syndrome [44].

Though the above rare variant gene changes incur large effect sizes and therefore strong linkage with ASD, their allelic frequency is low and they ultimately account for only a small proportion of ASD cases. Replication of many of these findings has also proved challenging [45]. With the advent of microarray analysis and the capacity for detection of copy-number variation (CNV) paving the way for genome-wide association studies [46], investigation of common variant genes (those with greater allelic frequency but smaller effect sizes) has yielded some positive results: chromosome 5p14.1 [47], the MACROD2 locus [48], and semaphorin 5A [49]. However, despite the significant advance of microarray analyses, replication of common variant analyses has proved difficult given insufficient powering of studies [48]. As a result, rare variant analyses remain a primary source of genetic data in ASD. Among the most readily replicated include the X-linked NLGN4 and NLGN3 genes along with interaction genes Shank 3 and Neurexin 1 [45], which are involved in encoding proteins regulating maturation and signaling in the excitatory synapse [50]. Though studies into the genetic basis of ASDs have yielded replicable results, these collected data account for a minority of ASDs, with the majority stemming from unclear etiology to date. It is hoped that further investigation of rare variant genes will yield insights into the specific neurobiology and pathogenesis of these illnesses, while advancing genomic techniques and more adequately powered studies will highlight common variant risk genes that compound phenotypic risk [47].

Using direct neuroradiological or neuropathological evidence or well-documented lesions from other cases with specific neuroanatomical or neurophysiological abnormalities, there has been a search for a lesion that underlies autism. Arguments for very specific, highly localized deficits (e.g., in facial recognition or processing of gaze) have been made as well as those that propose broader deficits in information processing and cognition that have less clear implications for neurobiology. Whatever the primary deficit or deficits in autism, these deficits must affect the way in which a child acquires information and skills from very early in development. In addition, the hypothesized deficits must allow for relative sparing of some domains (e.g., early gross motor development, sequence of development of syntax and lexical semantics, object permanence).

There is evidence for neuropathological changes in ASDs. Post-mortem studies have shown abnormalities in the cerebellum [51, 52], hippocampus, and amygdala [52]. Small studies have found a reduction in the size of cortical minicolumns, as well as an increased number of these minicolumns in both subjects with autism [53] and Asperger’s disorder [54].

In terms of structural studies of the brain in subjects with autism, a consistent finding is that young subjects with autism have larger brains than matched controls; more precisely, there appears to be an acceleration in brain growth that subsequently slows by late childhood [55]. Increased volume of the caudate nucleus in ASDs has been demonstrated and shown to correlate with the degree of restricted and repetitive behaviors [56]. Reductions in corpus callosum volume have also been demonstrated [57], as well as preliminary evidence for impaired neural connectivity of the corpus callosum and other white matter tracts via diffusion tensor imaging analyses [58]. Some magnetic resonance imaging (MRI) studies have demonstrated cerebellar vermal hypoplasia, but not all studies [59, 60]. This may be related partly to IQ effects on cerebellar morphology [61]. Other studies have found decreased cross-sectional area of the area dentata [62], increased amygdala volumes [55, 63, 64], as well as differences in cortical asymmetries [65]. MRI studies have revealed increased brain and lateral ventricular volume in autistic disorder [66].

Functional imaging studies, particularly fMRI, have had a profound impact on the understanding of autism neurobiology [67]. Though discussion of each series of findings is beyond the scope of this chapter, hypoactivation of the fusiform gyrus during face processing has been amongst the most reported findings [68]. Hypoactivation and impaired modulation of other complementary social brain regions, such as amygdala and the posterior superior temporal sulcus, have also been implicated [69]. Furthermore, those individuals with high-functioning autism have been demonstrated to have...
normal fusiform activation with familiar faces but impaired activation with unfamiliar faces, again hinting at the large phenotypic and neurobiological heterogeneity of autism spectrum disorders [70].

Positron emission tomography (PET) revealed generalized hypermetabolism in one [71] but not another study [72]. Investigations using PET scans on patients with infantile spasms found that 10 of 14 children who had bitemporal hypometabolism met criteria for an ASD at follow-up [73]. The same group [74] found asymmetries in serotonin synthesis in the brains of children with autism, as well as a global increase in cerebral serotonin synthesis capacity in children with ASDs (vs controls that show a steady decrease with age toward adult levels) [75]. Subjects with ASD show decreased activation in the amygdala while undergoing a facial processing task [76]. Magnetic resonance spectroscopy (MRS) revealed decreased levels of phosphocreatine and aATP in the dorsolateral frontal cortex [77].

Diagnosis

Phenomenology

There is much controversy associated with the diagnosis of autism. This is somewhat surprising at times as this seems to be largely related to the concerns about the growing ASD prevalence. Some have argued that increasing prevalence is due to changing diagnostic criteria. It is a bit ironic since the DSM-IV criteria have been in place for 20 years. Further, autism is one of the few psychiatric disorders for which there is agreement between the DSM and International Classification of Diseases (ICD) diagnostic classification systems. In fact, despite the concerns, the reliability and stability of the diagnosis of ASD is well established through the use of the widely accepted Autism Diagnostic Inventory-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). These are internationally acknowledged as gold standard instruments for research and clinical practice.

The central feature of the autism spectrum disorders is a disturbance of social development, including difficulty in developing meaningful attachments and social reciprocity [78, 79]. There is clearly some variation in the clinical presentation. Typically, a child with ASD has atypical patterns of eye contact and facial expression. Children with ASD are less apt to engage in these behaviors and are seemingly less able to coordinate expressive and receptive social cues. They also seem to lack empathy or the ability to perceive others’ moods or anticipate others’ responses. This may lead the child to act in a socially inappropriate manner or lack the social responsiveness necessary for success in social settings. These difficulties may result in subsequent difficulty in developing close, meaningful relationships. However, some youths with ASD eventually develop warm, friendly relationships with family even though their relationships with peers lag behind considerably.

Another area of difficulty for many children with ASD is in the acquisition and proper use of language for communication. It was previously estimated that only about one-half of children with ASD develop functional speech. However, the percentages may be larger as more high-functioning individuals with ASD are identified. If a child with ASD does begin to speak, their babble is decreased in quantity and lacks vocal experimentation. Yet, some children with ASD are loquacious; however, their speech tends to be repetitious and focused on preoccupations rather than aimed at maintaining reciprocity or engagement in a dialogue. People with ASD may use stereotyped speech including immediate and delayed echolalia, pronoun reversal, and neologisms. This is especially the case when the level of speech is limited. Even in individuals with higher functioning, speech may be idiosyncratic, consist of concrete constructions, include grammatical anomalies, lack or include atypical social meaning, and lack inference and imagination. For these individuals, the delivery of speech frequently includes atypical tone, pitch, and prosody (accent and cadence).

Individuals with ASD frequently engage in unusual patterns of behavior. They may resist or have significant difficulty with new experiences or transitions, to an extent much greater than their typical peers. At younger mental ages, they may engage in stereotyped motor behaviors. Classically, this has included hand flapping, peculiar finger movements (often in the periphery of the visual field), or rocking. Some children with autism engage in self-injurious behaviors, including biting or striking themselves, or banging their heads. Self-injury is most likely to occur in children with autism with moderate, severe, or profound mental retardation, but is also found in children with autism without mental retardation [80].

The play of children with ASD does not usually involve traditional toys or uses toys in atypical fashion. Play is often repetitive and may involve unusual preoccupations.

Individuals with ASD may have unusual sensitivity to some sensory experiences. This may include sensitivity in any of the five senses but particularly sound and touch. It is not clear whether these sensitivities have a neural substrate, are unusual habits, or if they reflect a resistance to unique or unexpected experiences in the environment.
Other problems in autistic disorder and other ASDs include deficits in shifting of attention and “joint attention.” [81, 82] “Joint attention,” or the ability to share one’s attention with another, typically develops by 12 months of age. At that developmental level, it is characterized by children shifting their gaze to follow verbal and nonverbal cues of the parent so they can share a visual experience. Children with ASD are often very delayed in developing joint attention, if they ever develop it all. Examples of joint attention include social exchanges that include pointing, referential gaze, and gestures showing interest. For those who do develop joint attention, the skill is usually not nearly as effective as it is in typical children.

Many children with ASD also have symptoms of hyperactivity and difficulty sustaining attention, but these must be distinguished from the joint attention deficits. It is not clear whether children with ASD can also have attention-deficit hyperactivity disorder (ADHD), although many children with ASD may meet diagnostic criteria for the latter condition.

For many years, it was thought that Asperger’s disorder was a condition distinct from autistic disorder as they share many common features. When originally describing the condition, Hans Asperger remarked that the children he studied began to speak at about the same time as typical children and eventually gained a full complement of language and syntax. However, he also observed that his patients had an exhaustive focus on particular topics. Asperger also described that the children he studied had difficulty in social reciprocity, and focused on certain interests excessively [83]. A DSM-IV diagnosis of Asperger’s disorder is made if criteria for social deficits and repetitive stereotyped interests and behaviors of autistic disorder are met, but language is normal at 3 years of age by history, and full criteria for autistic disorder are not met. Even with Asperger’s observations in mind, it is difficult to make the distinction between Asperger’s disorder and so-called “high-functioning autism.” And, given that there are no known biological (including genetic or functional and neuroanatomical imaging) differences between the conditions, the value of such a nosology is being questioned.

Rett’s disorder is a developmental disorder that occurs almost exclusively in females and typically differs substantially from autistic disorder after the toddler stage. Typically, the child with Rett’s disorder has an uneventful prenatal and perinatal course that continues through at least the first 6 months. With onset of the disease, there is typically deceleration of head growth, usually between 5 months and 4 years of age. In toddlerhood, the manifestations of Rett’s disorder can be similar to those of autistic disorder in that there is frequently impairment in language and social development along with the presence of stereotyped motor movements. In particular, there is loss of acquired language, restricted interest in social contact or interactions, and the start of hand wringing, clapping, or tapping in the midline of the body. Purposeful hand movement is typically lost. Another common symptom is hyperventilation. The child with Rett’s disorder actually may improve in social capabilities as time passes while progressively deteriorating in cognitive and motor function. The disorder is relatively easily differentiated from other ASDs after the child has reached the age of 4 or 5 years [84]. Mutations in the gene (MECP2) encoding X-linked methyl-CpG-binding protein 2 (MeCP2) have been identified as the cause of more than 80% of classic cases of Rett’s syndrome [44, 85]. Different mutations are likely responsible for much of the phenotypic variation seen in the disorder [86], including cases with preserved speech and normal head circumference [87].

Childhood disintegrative disorder and autistic disorder have some similarities in that they both involve deficits in social interaction and communication, as well as repetitive behaviors. However, the symptoms of childhood disintegrative disorder appear abruptly or over a few months after 2 years or more of normal development. There is generally no prior serious illness or insult although a few cases have been linked to certain organic brain ailments such as measles, encephalitis, leukodystrophies, or other diseases. With the onset of childhood disintegrative disorder, the child loses previously mastered cognitive, language, and motor skills and regresses to such a degree that there is loss of bowel and bladder control [13, 88]. Children with childhood disintegrative disorder tend to lose abilities that would normally allow them to take care of themselves, and their motor activity contains fewer complex, repetitive behaviors than in autism. Some children with this disorder experience regression that occurs over a period of time and then becomes stable. Another group of children afflicted with childhood disintegrative disorder have a poorer outcome with onset of focal neurological findings and seizures, in the face of a worsening course and greater motor impairment [89]. The vast majority of children with this disorder deteriorate to a severe level of mental retardation with a few retaining selected abilities in specific areas. Differential diagnosis of childhood disintegrative disorder requires obtaining a particularly thorough developmental history, history of course of illness, and neurological evaluation to rule out disorders including acquired epileptic aphasia (see “Differential Diagnosis” below).

Pervasive developmental disorder not otherwise specified (PDD NOS), or atypical autism, should be reserved for cases in which there are qualitative impairments in
reciprocal social development, communication, and imaginative and flexible interests, but criteria for a specific pervasive developmental disorder as described above are not met. It is important in the education of parents, teachers, and colleagues to be clear that PDD NOS is closely related to autistic disorder, since many families that have been given diagnoses of autistic disorder and PDD NOS have the mistaken impression that this represents strong diagnostic disagreement between clinicians.

At the present time, it would appear that among autistic disorder, Asperger’s disorder, childhood disintegrative disorder, and pervasive developmental disorder, there is a distinction without a difference. That is, it is not clear that these are distinct entities. As a result, the current nomenclature appears to encompass all these conditions under the rubric of “autism spectrum disorder” (ASD) (Table 21.1).

Given that this is a “spectrum” disorder, it suggests the possibility that the symptoms of ASD fall along a spectrum from extreme to mild impairment. However, this model can be further elucidated by examining several spectra (Figure 21.1).

**Differential Diagnosis**

The diagnosis of ASD requires distinguishing amongst several disorders that consist of deviations in socialization, language, and play. One systematic approach would be to examine the course of the patient from birth and determine if there was ever a period of normal development. Disorders to be considered in the differential diagnosis include developmental language disorder, intellectual disability, acquired epileptic aphasia (Landau–Kleffner syndrome), schizophrenia, selective mutism, psychosocial deprivation, and other conditions, as listed in Table 21.2.

Children with developmental language delay and sensory deficits can appear to have symptoms related to ASD at early ages. Due to their language deficits, these children may seem to have communication problems, and may be socially immature. However, children with language delay use relatively normal patterns of language, engage in imaginative play, and demonstrate appropriate attachment behaviors and social interactions with family and friends [90]. These children do not tend to have obsessive interests, or restricted and repetitive behaviors like those seen in children with ASD. They also do not respond unusually to sensory experiences as children with autism frequently do [91].

Approximately one-half of severely and profoundly mentally retarded children have symptoms consistent with ASD; it is unclear whether this is due to a high rate of ASD in this group or a consequence of severe and profound mental retardation having some phenomenological overlap with ASD, at least in terms of the

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**Figure 21.1** What are the Elements of the ASD Spectrum?
<table>
<thead>
<tr>
<th>Table 21.1</th>
<th>DSM-IV diagnosis of autistic disorder and other pervasive developmental disorders.</th>
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<tbody>
<tr>
<td>Autistic Disorder</td>
<td>Rett’s Disorder</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>Delays or abnormal functioning in social interaction, language, or play by age 3 years</td>
</tr>
<tr>
<td><strong>Social Interaction</strong></td>
<td>Qualitative impairment in social interaction, as manifested by at least two of the following:</td>
</tr>
<tr>
<td></td>
<td>a) marked impairment in the use of multiple nonverbal behaviors, i.e., eye-to-eye gaze, facial expression</td>
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<td></td>
<td>b) failure to develop peer relationships appropriate to developmental level</td>
</tr>
<tr>
<td></td>
<td>c) lack of spontaneous seeking to share enjoyment, interests, or achievements with other people</td>
</tr>
<tr>
<td></td>
<td>d) lack of social or emotional reciprocity</td>
</tr>
</tbody>
</table>

(Continued)
Table 21.1. (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Autistic Disorder</th>
<th>Rett’s Disorder</th>
<th>Childhood Disintegrative Disorder</th>
<th>Asperger’s Disorder</th>
<th>Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS)</th>
</tr>
</thead>
</table>
| Communication           | Qualitative impairments of communication as manifested by at least one of the following:  
  a) delay in, or total lack of, the development of spoken language (without attempt to compensate with gesture)  
  b) marked impairment in initiating or sustaining a conversation with others in individuals with adequate speech  
  c) stereotyped and repetitive use of language or idiosyncratic language  
  d) lack of varied, spontaneous make-believe or imitative play appropriate to developmental level | Severely impaired expressive and receptive language development with severe psychomotor retardation | Qualitative impairment in communication along with loss of expressive or receptive language | No clinically significant delay in language (single words by age 2 and communicative phrases by 3 years) |
| Restricted and repetitive interests | Loss of previously acquired purposeful hand movements with the subsequent development of stereotyped hand movements; appearance of poorly coordinated gait or trunk movements | Restricted, repetitive and stereotyped patterns of behavior with loss of bowel or bladder control, play motor skills previously acquired | Same as Autistic Disorder |

**Exclusions**

Disturbance not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

Disturbance not better accounted for by another PDD or Schizophrenia

Criteria are not met for another PDD or Schizophrenia
Table 21.2  Differential diagnosis of autistic disorder and other pervasive developmental disorders (PDDs).

<table>
<thead>
<tr>
<th>Disorder or Condition</th>
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</thead>
<tbody>
<tr>
<td>Developmental language disorder</td>
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<tr>
<td>Mental retardation</td>
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<tr>
<td>Acquired epileptic aphasia (Landau–Kleffner syndrome)</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
</tr>
<tr>
<td>Chromosome 15q11-13 duplication</td>
</tr>
<tr>
<td>Schizophrenia</td>
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<tr>
<td>Selective mutism</td>
</tr>
<tr>
<td>Psychosocial deprivation</td>
</tr>
<tr>
<td>Hearing impairment</td>
</tr>
<tr>
<td>Visual impairment</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Metabolic disorders (inborn errors of metabolism, e.g., phenylketonuria)</td>
</tr>
</tbody>
</table>

presence of developmental delays. Individuals with profound intellectual disability, without an ASD, usually have social skills consistent with their mental age, in sharp contrast to the individual with ASD, whose social skills are always delayed.

Acquired epileptic aphasia (Landau–Kleffner syndrome) is very rare compared to autistic disorder and other ASDs. A high index of suspicion for this disorder is raised by the loss of phrase speech after the age of 24 months, with EEG confirmation. Since the typical regression associated with ASD occurs before 18 months of age, children with language regression between 18 months and 30 months should also be evaluated by EEG, preferably with unmedicated sleep, to rule out an atypical acquired epileptic aphasia syndrome. The diagnosis of acquired epileptic aphasia is important because language may return after anticonvulsant or corticosteroid treatment [92].

Schizophrenia is differentiated from autism on the basis of symptom presentation. While some children with autism may have disorganized speech or behavior, they will not exhibit the hallucinations or delusions that characterize childhood schizophrenia. In terms of thought processes, higher functioning people with ASD tend to be ruminative, and may be so preoccupied as to appear illogical or thought disordered. Again, however, delusions and hallucinations will not be present, except in rare cases in which older adolescents or young adults with autism develop schizophrenia.

In selective mutism, the child is unable to speak in certain situations. As in ASD, the child may seem socially isolative and nonresponsive to environments outside the home. The child with selective mutism usually can converse with family members and engage in imaginative play. Some selectively mute children do have articulation problems and/or language delay, but do not have deviations of speech such as those found in children with ASD [93].

Children with severe psychosocial deprivation can present with broad language deficiencies, stunted social development, and odd motor movements and habits [94]. However, this triad is qualitatively distinct from that seen in autistic disorder. Fortunately, many children subjected to extreme neglect, even over periods of years, can resume the developmental process at a rapid rate when exposed to nurturing and stimulating surroundings [95]. A child with a significant abuse and/or neglect history, as well as other children, should not be presumed to have ASD unless a diligent assessment, as described below, has been completed.

Course and Natural History

The general course of ASD is one of improvement over time. While the developmental trajectory may have a slope considerably less than that of a typically developing child, children with ASD do improve.

Assessing the course of ASD is complicated by comorbidity, especially the presence of intellectual disability and language problems. As a result, development expectations or a prognosis must control for these issues. And, with the growing awareness of higher functioning individuals, it seems clear that the ultimate capacity for semi-independent or even independent living in the community is a real possibility.

Just because a child has ASD does not mean that they have stopped developing. Indeed, in general, as children with ASD grow older, some of the more “classical” symptoms of the disorder also change. Even those children with lower functional levels, who appear completely socially removed, with virtually no speech or only echolalic speech, motor stereotopies, and little ability to adapt to change, most often improve. As children with ASD enter the school years, the echolalic speech patterns lessen and more spontaneous communication begins to appear – this may even include spontaneous speech. In addition, there will likely be a growing tolerance of being around and even beginning to play with other children. Furthermore, social relationships, even if impaired or idiosyncratic, begin to appear.

As the child gets older, many of the bothersome behaviors appear to subside. These include a decrease in stereotyped movements such as rocking or spinning. However, as the child with ASD learns to adjust to the demands or expectations of daily living, frustration with
being required to disrupt routines or a limited ability to communicate wants and needs, may lead to behavioral disruptions. This is exacerbated by the fact that idiosyncratic interests and ritualistic behaviors can and often do persist into adolescence and adulthood. In terms of language, receptive and expressive abilities can gradually improve over the adolescent years [35, 80, 96–99].

With the advent of adolescence comes a new set of challenges. Not only do the changes associated with puberty add new challenges to the child and family facing ASD, but increased body size and a more adult appearance make previous “childish” behaviors seem far more awkward or even dangerous. In some adolescents, however, there is an increase in aggression with the onset of puberty; if this occurs, a reassessment of the child is essential, including an EEG, as there is an increased possibility of seizures appearing in this age group, and significant regression may accompany this epileptic activity.

Aspects of puberty such as sexual drive and menstruation are complex but can be managed with appropriate educational and behavioral interventions. Many individuals with ASD do not understand the social implications of sexuality, such as masturbation, nudity, and touching, as well as other sexual behaviors. They are also more vulnerable to the sexual advances of predatory adolescents or adults. Therefore, anticipatory guidance and planning are important.

With maturity, and especially with the advent of adolescence, higher functioning individuals with ASD may become aware of the fact that they differ significantly from their peers. They often develop some interest in others and a desire to make friendships, but they often lack the “know-how” to accomplish this. This may lead to demoralization and even depression.

Previous follow-up studies of children with ASD (largely in children with “classical” or “Kanner” autism) into adulthood show that approximately two-thirds remain seriously impaired and are incapable of catering for their own needs. This earlier experience suggested that many of these individuals live in protected home-based or longer-term residential settings during their adult years, including community-based group homes. Between 5% and 17% of autistic adults are able to work with minimal support. In spite of social improvement in about one-half of children with autism over periods of years, most autistic individuals have abnormal social relationships. Outcome in autism is largely determined by IQ and language abilities, with IQ being the most powerful predictor. Good or fair outcomes are almost always associated with full-scale IQs of greater than 60. Acquisition of useful speech by 5 years of age is another important predictor of positive outcome. Even when an individual has an IQ and language abilities within a relatively normal range, there is nearly always residual social impairment that is persistent into adulthood.

There is a pressing need for follow-up studies on the newly identified, higher functioning individuals with ASD. Given recent reports that perhaps as many as two-thirds of ASD youth may live in the community and participate in regular education without services, the likelihood of a more successful, long-term adaptation is probable. However, even for higher functioning individuals with ASD, it is unusual for an autistic adult to marry or sustain a long-term sexual relationship. But, the possibility of having friends, a social life, and living independently is quite realistic.

**Evaluation**

As with all careful evaluations, the diagnostic process for an individual with a suspected ASD begins with careful history-taking, as well as the collection of data about behavior, cognitive abilities, and developmental functioning. Appropriate sources for this information include parents, teachers, and anyone who has had meaningful contact with the child. Other means of obtaining needed information include direct observation of the child and standardized assessment. A crucial step in evaluating developmental disorders lies in procuring a solid account of the developmental history. Special heed should be taken with regard to developmental phases of language, social interactions, and play [78]. Also, investigation of any chronic illnesses or illnesses with a neurological bearing in the child, as well as the medical history of the family, should be performed. Clinicians should inquire about family history of neurological disease, psychiatric disorder, history of developmental delay, and social, language, and learning problems.

Structured interviews are available for use in evaluating children specifically for autism, which help clinicians collect and organize historical information in a reliable manner. One such instrument is the Autism Diagnostic Interview-Revised (ADI-R), which is a standardized, semi-structured interview that can be administered to parents to help determine if the child has an ASD [79].

An essential piece of the overall evaluation is gained through direct observation of the child. Ideally, this should be done in a variety of settings to obtain an overall view of the child’s behaviors and functioning under differing environmental conditions. The Autism Diagnostic Observation Schedule (ADOS) is recommended to structure observation of children, adolescents, and adults with suspected autism [100]. There are also a variety of other instruments available for evalua-
tive purposes, including the Childhood Autism Rating Scale [101] and the Autism Behavior Checklist [102]. Another useful instrument is the Aberrant Behavior Checklist-Community Version (ABC-CV), which is useful for following responses of irritability and hyperactivity to interventions [103].

A complete physical examination, including a thorough neurological exam, is an essential component of any evaluation. It is important to identify and treat any medical and dental problems that contribute to or exacerbate a child’s psychiatric symptoms. Overall physical health should be assessed and particular attention should be paid to those findings that could be related to ASD. For instance, cardiac and other congenital physical anomalies should be noted, and a skin (visual and Wood’s lamp exam) and dysmorphology exam should be done to search for lesions consistent with genetic, metabolic, or structural disorders. All children with speech delay or articulation problems should have audiological testing, as even subtle hearing loss can adversely affect social and language development. Vision testing should be performed if there is any suggestion of visual deficit. There are no specific diagnostic laboratory tests for autism. A high index of suspicion should be maintained for seizure disorder. Specialized laboratory tests are warranted only with specific indications, but these might include chromosomal analysis, amino acid studies, and/or EEG. Although one-quarter of children have nonspecific findings on structural neuroimaging scans, MRI should only be performed if there are findings from the history and physical examination that suggest a potentially treatable structural lesion.

Chromosomal studies are indicated for children with a history and physical examination suggestive of fragile X syndrome or other specific chromosomal abnormalities. Although genetic counseling, including chromosomal analysis to exclude fragile X syndrome, interstitial 15q11q13 duplications, and other chromosomal anomalies, is most obviously indicated for families considering a subsequent pregnancy, 25% of the boys born to maternal aunts of children with fragile X syndrome will have fragile X syndrome. Currently, there is no specific treatment for fragile X syndrome or duplications of the Prader-Willi/Angelman syndrome region of chromosome 15, but chromosomal testing will have implications beyond genetic counseling if treatments are developed for these disorders in the future.

Complex neuroimaging studies, EEG, and other laboratory procedures have been recommended during the course of evaluation of an individual with ASD. In general, these are not indicated, unless there are specific clinical indicators for such evaluations (Table 21.3).

Psychological Testing

Psychological testing is a useful adjunctive procedure in the diagnosis of ASD. It provides details of the clinical picture that facilitate development of intervention programs while also providing benchmarks for monitoring developmental and treatment progress.

Psychological testing never stands alone as conclusive evidence of an individual’s skills. The most useful measures are those that yield data about adaptive functioning, language skills, and intelligence. Testing can include the full spectrum of cognitive assessments, but since language deficits are so common in ASD, careful examinations should include both verbal and nonverbal cognitive measures – for example, Merrill-Palmer Scale [104], Leiter International Performance Scale [105], Bayley Scales of Infant Development [106], and Differential Abilities Scales [107]. The measures used depend on the individual being assessed, as well as the skill and experience of the examiner.

Other psychological testing may include assessments in other areas, including neuropsychological testing. For many children, examination for learning disabilities and comorbid psychopathology may be crucial. Since psychological testing instruments are not normed for use in individuals with ASD, the validity of the results of such testing must be considered before utilizing the data for diagnosis, treatment planning, or other purposes.

Objective measures of the capacity of an individual to utilize their skills to meet the demands of everyday life appear to be crucial in the assessment of individuals with ASD. Because cognitive and language measures may underestimate skills, reports of the skills necessary for self-care and daily living are very useful. While there are many instruments used in the assessment of so-called “adaptive skills” or “activities of daily living,” the Vineland Adaptive Behavior Scales [108, 109] are the well-validated standard that provides valuable information about adaptive functioning so necessary for treatment planning and monitoring.

Goals of Treatment

The treatment of ASD has become progressively more complex. Historically, attempts were made to treat autism with psychoanalytic interventions. There remains little evidence that these psychoanalytic or other traditional insight-oriented psychotherapies are beneficial in the treatment of ASD. In more recent years, the treatment strategies have focused on the symptoms of ASD, and the goal of therapy has shifted from “cure” to optimizing adaptive functioning. As a result, behavioral treatments have had increasing prominence in the treat-
ment of ASD [110]. Unfortunately, behaviors learned by children with autism in one particular setting are not necessarily carried over to other contexts or retained well [111]. As a result, it appears that a group of interventions linked together appear to have the most promise for most individuals with an ASD.

Autism spectrum disorders are chronic disorders with a changing course requiring long-term intervention with implementation of various treatments at different points in time. Given that there is no current cure for ASD, treatment must be individualized and have both short-term and long-term goals for the individual and his/her family. Rutter has defined treatment in terms of four quintessential aims. These include the following:

1. The advancement of development, particularly regarding cognition, language, and socialization.
2. The promotion of learning and problem-solving.
3. The reduction of behaviors that impede the learning process.
4. The assistance of families coping with autism.

Since these aims are broad, it is useful to further differentiate them in terms of immediate and long-term needs. Each goal likely will require a distinct plan of its own and even a unique set of clinical skills to address the manifold complexities associated with ASD (Table 21.4). Most effective plans use community-based rather than residential treatment resources, as institutional settings tend to limit the experiences necessary to optimize functioning for living in a more typical social setting. This can usually be accomplished, except in

<table>
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<tr>
<th>Table 21.3</th>
<th>Suggested components of an evaluation of suspected autism.</th>
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<tr>
<td><strong>History</strong></td>
<td>Sources: parents, teachers, other caregivers, anyone with regular meaningful contact</td>
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<tr>
<td></td>
<td>Developmental history – semi-structured interview with primary caregiver(s) strongly suggested: Autism Diagnostic Interview-Revised (ADI-R)</td>
</tr>
<tr>
<td></td>
<td>Past medical history</td>
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<td></td>
<td>Family history</td>
</tr>
<tr>
<td><strong>Examination</strong></td>
<td>Direct observation of child’s social, communication, and imaginative skills</td>
</tr>
<tr>
<td></td>
<td>Autism Diagnostic Observation Schedule (ADOS) suggested</td>
</tr>
<tr>
<td></td>
<td>Psychological testing (nonverbal and verbal intellectual testing)</td>
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<td></td>
<td>Speech and language evaluation</td>
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<tr>
<td></td>
<td>Tests of adaptive functioning: e.g., Vineland Adaptive Behavior Scales</td>
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<tr>
<td></td>
<td>Vocational Assessment</td>
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<tr>
<td></td>
<td>Physical examination including particular attention to the neurological examination, dysmorphology examination, and examination of the skin (preferably with a Wood’s lamp to rule out hypopigmented macules of tuberous sclerosis)</td>
</tr>
<tr>
<td></td>
<td>Audiological testing</td>
</tr>
<tr>
<td><strong>Laboratory testing</strong></td>
<td>Lead level</td>
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<td></td>
<td>Quantitative urinary amino acids</td>
</tr>
</tbody>
</table>

**Other tests depending on clinical situation**

- EEG if suspicion of history of possible seizures or speech regression after 24 months
- Chromosomal analysis and fragile X DNA testing if dysmorphology, family history of chromosomal disorders, or as part of genetic counseling
- MRI if findings in history or examination to suggest potential therapeutic yield
- Other laboratory testing based on findings from history and physical examination (e.g., organic acids, thyroid function tests, etc.)

<table>
<thead>
<tr>
<th>Table 21.4</th>
<th>Goals for treatment.</th>
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<tr>
<td><strong>Advancement of normal development, particularly regarding cognition, language, and socialization</strong></td>
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<tr>
<td><strong>Promotion of learning and problem-solving</strong></td>
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<tr>
<td><strong>Reduction of behaviors that impede learning</strong></td>
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<tr>
<td><strong>Assistance of families coping with autistic disorder</strong></td>
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<tr>
<td><strong>Treatment of comorbid psychiatric disorders</strong></td>
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times of extreme stress or need, when a child could benefit from respite care or brief hospitalization. Effective treatment often entails setting appropriate expectations for the child and adjusting the child’s environment to foster success [78].

Approach to Treatment

Individuals with ASD require diverse treatments and services simultaneously, at various levels, and across the lifespan [112]. This complexity demands that a single individual becomes the primary clinician who serves as a coordinator of services. All too often this role is relegated to parents; however, even the most well-informed parent needs assistance in “directing the traffic.” The primary clinician should have regular contact and visits with the child and his or her caretakers in order to assess the individual needs of the child while establishing a therapeutic alliance not only with the child but also the “team” invested in the child’s (or adult’s) care. An effective approach often calls for the services of a number of professionals working in a multidisciplinary, collaborative team. This group may include psychiatrists, pediatricians, psychologists, pediatric neurologists, special educators, speech and language therapists, behavior therapists, occupational therapists, physical therapists, social workers, and a myriad of other specialized therapists.

Psychosocial Interventions

Some of the most beneficial interventions for children with autism have been achieved through the educational process. With the passage in the United States of the Education for All Handicapped Children Act of 1975 (Public Law 94-142) and the subsequent IDEA (Individuals with Disabilities Education Act), all handicapped children, including those with ASD, are guaranteed the right to a free, appropriate public education in the least restrictive environment (LRE). This right is guaranteed notwithstanding the severity or nature of the child’s disability. Improvement in the educational experience afforded children with ASD in recent years has resulted in fewer children requiring long stays in institutional settings [113]. With regard to lower functioning or severely intellectually disabled children with autism, no single educational approach has been identified as superlative in improving a specific area of weakness.

A debate has been ongoing during the last several years regarding the issue of mainstreaming of handicapped children within the schools. Although there has been a move toward implementation of mainstreaming, many children with ASD remain in specialized classrooms with children of similar need for intensive language and behavioral management services. Many children with ASD will be able to function academically or behaviorally at their best if placed totally within a regular classroom setting with no other supports. However, there can be distinct advantages in the placement of mild-to-moderately functioning children with ASD in a regular classroom for at least part of the day. These benefits include social exposure to typical children and greater intellectual stimulation.

Curricula that encourage and teach appropriate communications benefit the majority of children with ASD. This can be done individually with even very young children, and also can involve teaching parents and others how to foster effective communication in a child with ASD. Behavioral techniques derived from operant conditioning theory are used routinely by teachers and clinicians working with children with autism. Reinforcing positive behaviors, not reinforcing unwanted behaviors, and using simple techniques to replace an undesirable behavior with a more adaptive one are standard behavioral procedures. Organizing a milieu that is predictable and promotes understanding and learning for the child with ASD often alleviates the need for intensive behavior programs.

Success has been achieved in placing adults with ASD in jobs and workshops in the community. How successful one is in securing a job for an adult with ASD often depends on the resources in the community, and the ability of the adult’s parents or others to advocate for them. Work placement and training as well as encouragement and consistent support on the job have contributed to success in the workplace for the individual with ASD.

Depending on the specific needs of the individual autistic child, a child can benefit from many different therapies or interventions. Among these are speech and language therapy, occupational therapy, and physical therapy. Some programs offer art and/or music therapy as a means of encouraging communication and self-expression. Brief individual psychotherapies—especially structured treatments like cognitive behavioral therapy (CBT)—may be helpful to those who are verbal and have a focused problem or are experiencing symptoms of anxiety or depression. Social skills groups or training may be especially beneficial for higher functioning children, adolescents, and adults. These interventions can serve to give the individual social experience in a positive, supportive setting.
**Doctor-Patient Relationship**

As with any clinical relationship, respect for the patient is the cornerstone of assessment and treatment. And while many patients with ASD have difficulty establishing and maintaining social relationships, they can and do benefit from relationships with their clinicians. It is incumbent upon the physician and other clinicians to come to understand the unique likes and dislikes of their patients and to be able to respond accordingly. Individuals with ASD can even have a sense of humor, albeit quirky, at times. Appreciating this and other unique qualities of each patient with ASD improves the overall relationship with the patient and the quality of care.

Many of the difficulties faced by persons with ASD are not a consequence of their own lack of empathy but the lack of sensitivity to the unique problems of ASD shown by those around them. In many ways, this stems from the adverse feelings that are all-too-often directed at individuals with culturally defined “defects.” [114] Not only must the clinician be sensitive to these issues but also it is equally important that family members, teachers, and others help their community to have a proper perspective on individuals with ASD and not to respond out of fear or prejudice. Irrespective of the presence or absence of any diagnosis, we are all sensitive to how we are treated by others; this is true for most individuals with ASD. One must be cognizant that drives for mastery, development of autonomy, and acceptance are not reduced by the presence of an ASD.

**Family Support**

Having a child with ASD poses many complex challenges to all members of the family. As a result, even the strongest families will benefit from a broad spectrum of supports. Certainly, this support begins with the primary clinician and all the members of the clinical team; however, it should also include other members of the community. It is important to help families build bridges to community services in areas such as recreation and participation in religious activities. In many instances, families (both nuclear and extended) need to be taught about ASD and how to help a child (or adult) with ASD.

In some cases, the stresses or demands on a family may be sufficiently destabilizing that some form of structured family therapy may be necessary. Helping families deal with frustration, disappointment, fear, and ambivalence with regard to their handicapped family member is essential. Other crucial steps include aiding families in arranging for special services or respite care in addition to providing behavior management techniques and emotional support. Many individuals with autistic disorder and their families access support and services through local and national organizations. Such agencies include the Association for Retarded Citizens, Autism Society of America, Autism Speaks, and other community support groups. Books are also available to assist families [115] and peers [116] in learning about pervasive developmental disorders and to assist families in adapting to having a child with autistic disorder [117].

**Pharmacotherapy**

Even though ASD is considered to be a largely biological disorder, biological interventions in the form of medications have mostly proven to be of limited utility. Indeed, there is no pharmacotherapy that is specifically directed at treating the ASD syndrome. However, there are treatments that may be useful for the treatment of some of the symptoms of ASD and to help sustain behaviors to support other behavioral and environmental interventions. In short, pharmacotherapy is an adjunctive treatment for ASD.

For a long time the number of adequately controlled and powered psychopharmacological treatment trials in ASD has been limited. There are only two pharmacological agents with FDA-approved labeling specific for the treatment of ASD, and both target the “irritability” associated with ASD and not the specific syndrome itself. This is problematic, because many of the symptoms commonly seen in ASD (rituals, aggressive behavior, and hyperactivity) are also common in other individuals with developmental disorders such as intellectual disability without a pervasive developmental disorder. While these symptoms are clearly disruptive and problematic, they do not appear to be unique to ASD. As a result, some of the treatment strategies currently employed are derived from studies of other neuropsychiatric conditions with similar symptoms, including ADHD and OCD.

It is important to remember that the current state of the art is empirical treatment of target symptoms. Some parents and teachers of children with autistic disorder may have the misconception that medication can eliminate core social and cognitive dysfunction. There is no pharmacological substitute for appropriate educational, behavioral, communication, vocational, and recreational programming. It is essential to remember and remind parents, teachers, and others that medication should always be seen as an adjunct to the core interventions that address the primary developmental challenges associated with these disorders.

The use of medications to treat ASD appears to have significant potential as an adjunct to educational, environmental, and social interventions. Regrettably, there
is no diagnosis-specific treatment at present. Nonetheless, individuals with ASD still have significant impairments as well as the all-too-often forgotten potential to gain skills and levels of functioning compatible with living in the community. It is a reasonable goal for clinicians to adopt the judicious use of psychopharmacological agents to assist in this adaptation. As one prepares for psychopharmacological treatment, we have found six principles to be useful:

(1) Environmental manipulations, including behavioral treatment, may be as effective, if not more effective, than medication for symptom treatment. Medications should be used as a part of an integrated environmental and medical treatment program.

(2) It is essential that the living arrangement for the individual being treated is capable of safely and consistently administering and monitoring the medication to be used.

(3) Individuals with ASD, when compared to the general population, are at as much, if not greater, risk for additional DSM-IV Axis I disorders/diagnoses. If a comorbid Axis I disorder is present, standard treatment for that disorder should be considered.

(4) There must be an established way of specifically monitoring the response to treatment over time. Side effects are common and mechanisms for identifying and reporting them must be established especially for those individuals with ASD least able to communicate them.

(5) A careful assessment of the risk-benefit ratio must be made before initiating treatment and, to the extent possible, the patient’s caretakers and the patient must understand the risks and benefits of the treatment.

(6) The risk-benefit ratios change over time and thus must be regularly reassessed over the course of treatment.

Potent Selective Serotonin Reuptake Inhibitors (SSRIs)

This class of agents includes selective and potent serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram), as well as the less selective but potent clomipramine, a tricyclic antidepressant. This group of medications is most effective when insistence on routines or rituals is present to the point of manifest anxiety or aggression in response to interruption of the routines or rituals [118–122], or after the onset of another disorder such as major depressive disorder or obsessive-compulsive disorder [123]. The common side effects associated with SSRIs are motor restlessness, insomnia, elation, irritability, and decreased appetite, each of which may occur alone or, more often, together. These side effects are usually dose-related; however, for unclear reasons (perhaps having to do with the well-replicated findings of serotonergic dysmodulation in ASD), there is very wide variation in the dose that this population can tolerate before these side effects emerge [124]. Because many of the side effects may be present as symptoms in the often cyclical natural course of ASD when medication is not present, the emergence of new symptoms, a different quality of the symptom, and occurrence of these symptoms in a new cluster are clues that the symptoms are side effects of medication rather than part of the natural course of the disorder [118]. Until genetic variation or some other marker is discovered that allows us to predict the final dose, it is best to begin at a very low dose in this population, and raise the dose in a forced titration fashion. When the dose-related side effects are encountered, the dose should be decreased to the highest previously tolerated dose [124].

Stimulants

It was long considered that stimulants were not appropriate in the treatment of ASD in spite of the fact that attentional problems are quite common. Small but significant reductions in hyperactivity ratings may be seen in children with ASD in response to stimulants such as methylphenidate [125], dextroamphetamine, and pemoline. In a placebo-controlled crossover study, 8 of 13 subjects showed a reduction of at least 50% in ADHD symptoms when treated with methylphenidate [126]. More recent studies have suggested that methylphenidate is clearly effective in reducing hyperactivity and inattention in individuals with ASD – perhaps as effective as it is in treating ADHD, alone [127]. Of course, stimulants are not without side effects. It has been reported that stereotypies may worsen, and irritability and dysphoria may appear in association with the treatment with stimulants. Similarly, as with other patients treated with stimulants, sleep and appetite disturbances may appear or worsen – this is particularly problematic in ASD when these symptoms may already be problematic.

A key distinction in assessing attentional problems of children with autistic disorder is the distinction between poor sustained attention (characteristic of children with ADHD) and poor joint attention (characteristic of children with autistic disorder). Problems in joint attention require educational and behavioral interventions or treatment of compulsions or rituals with SSRIs. Problems in maintenance of attention of the type seen in ADHD are more likely to respond to stimulants.
Atypical Neuroleptics Because of the positive response of many children with autistic disorder to typical neuroleptics, similar medications with reduced risk of extrapyramidal symptoms must be considered. In addition, atypical neuroleptics are often effective in treating the negative symptoms of schizophrenia, which seem similar to several of the social deficits in autistic disorder. However, although atypical neuroleptics have seen increased use, they also have side effects that are highly undesirable.

Initially, both risperidone and olanzapine showed promise in open-label trials in reducing hyperactivity, impulsivity, aggressiveness, and obsessive preoccupations [142–145]. A large double-blind, placebo-controlled study found risperidone to be more effective than placebo in the treatment of repetitive behavior, aggression, and irritability [120, 146], and these gains appear to hold up over time [147]. Weight gain has been a significant problem in longer-term studies [148]. Open-label outcomes with olanzapine for similar target symptoms have been mixed, with positive results being found by some [142, 145], but not others; [149] weight gain was also a severe problem in these studies. The perceived effectiveness of these medications coupled with the problems with weight gain have led some to look at ziprasidone (which is not thought to cause weight gain) in this population. In one study [150], a retrospective chart review was undertaken of adult subjects who had been on an atypical agent and were then switched to the atypical ziprasidone. Seven of ten subjects did better or as well on ziprasidone, and there was a net weight loss. Another study with youths also found positive outcomes in 6 of 12 subjects with autism and also reported no weight gain. However, ongoing concern about QTc prolongation exists for ziprasidone without more safety data for children and adolescents in general and ASD more specifically. More recently, controlled trials of aripiprazole have shown promise in treating ASD. In a recent study, Owen et al reported on a 8-week double-blind controlled trial in 98 patients and controls. Aripiprazole showed a significant improvement in reducing irritability starting in week 1 and persisting through the 8 weeks. However, twice as many patients on active drug had adverse events and discontinuation (10.6% vs. 5.9%), with extrapyramidal symptoms occurring in 14.9% of patients (cf. 8% on placebo). Further, there was a 2 kg weight gain in 8 weeks for the treatment group versus 0.8 kg in the placebo group [151].

The promises and challenges of using the atypical neuroleptics in the treatment of ASD are manifold. While they are quite effective in treating irritability and aggression and may work when nothing else seems to
help, the side effects are legion and problematic in the long term. Therefore, these should be seen as agents used for short-term, focused interventions while behavioral and other strategies are put into place. If they must be used longer term, then careful monitoring for weight gain and metabolic syndrome are an essential part of the treatment.

**Anticonvulsants**

Seizures are reported in 25% to 33% of patients with ASD. As a result, a significant number of ASD patients may be on anticonvulsants at some point in time. However, in addition to their antiepileptic properties, the anticonvulsants are potent psychotropics that have been shown to stabilize mood in patients with mood disorders. Since problems with emotional/mood regulation may be present in ASD, the psychopharmacological management of patients with ASD may include anticonvulsants [33]. Unfortunately, very few studies have been undertaken in this area. In an open trial of divalproex, 10 of 14 patients responded favorably, including improvements in affective stability, impulsivity, and aggression [152].

Barbiturates (e.g., phenobarbital) should be avoided, when possible, because barbiturates have been associated with hyperactivity, depression, and cognitive impairment; they should be changed to an alternative drug, depending on the seizure type [153, 154]. In addition, phenytoin (Dilantin) is sedating and causes hyper trophy of the gums and hirsutism, which may contribute to the social challenges for people with ASD.

Carbamazepine and valproate may have positive psychotropic effects, particularly when cyclical irritability, insomnia, and hyperactivity are present. Several children with ASD were treated with valproic acid after electroencephalographic abnormalities were found. These children had an improvement in behavioral symptoms associated with autistic disorder after valproate treatment [155]. Oxcarbazepine may have some of the positive psychotropic effects of carbamazepine, with less risk of agranulocytosis, but concern about uncommon hypoaemia remains. Similarly, reports of side effects including polycystic ovary syndrome have been associated with valproate. As a result of these side effects, other, newer anticonvulsants have been proposed for ASD individuals. However, lack of adequate clinical trials and many side effects leave the assessment of risk-benefit of such treatment to the individual practitioner and patient.

**Naltrexone**

The opiate antagonist naltrexone was suggested as a specific treatment for ASD. However, double-blind trials have suggested that naltrexone has little efficacy in treating the core social and cognitive symptoms of autistic disorder [156]. Naltrexone has also been suggested for the treatment of self-injurious behavior in ASD, although the controlled data are equivocal [156, 157]. Controlled trials have shown a modest reduction in symptoms of hyperactivity and restlessness sometimes associated with ASD [156, 158, 159]. Potential side effects include nausea and vomiting. Naltrexone may have an adverse effect on the outcome of Rett’s disorder, on the basis of a relatively large, randomized, double-blind, placebo-controlled trial [160].

**Lithium**

Adolescents and adults with ASD often exhibit symptoms in a cyclic manner and so there is much interest in how these patients might respond to agents typically used in bipolar disorder. A single open trial of lithium revealed no significant improvement in symptoms in patients with ASD without bipolar disorder [161].

**Anxiolytics**

Benzodiazepines have not been studied systematically in children and adolescents with ASD. However, their use to reduce anxiety in short-term treatment, such as before dental procedures, is similar to their use in the management of anxiety in people without ASD. One open-label study found a decrease in anxiety and irritability in patients receiving the anxiolytic buspirone [162].

**Glutamatergic Antagonists**

Interest in these agents has been sparked by the hypothesis that ASD may be a disorder of hypoglutaminergic activity [163]. In a double-blind, placebo-controlled study of the glutamatergic antagonist amantadine hydrochloride, there were substantial improvements in clinician-rated hyperactivity and irritability, although parental reports did not reach statistical significance (which may have been partially due to a strong placebo response) [164]. Further study of this medication and consideration of this hypothesis is warranted.

**Pyridoxine and Dietary Supplements**

Pyridoxine, the water-soluble essential vitamin B₆, has been used extensively as a pharmacological treatment in ASD. In the doses used for ASD, it is not being used as a cofactor for normally regulated enzyme function or as a vitamin; rather, it is used as a pharmacological agent to modulate the function of neurotransmitter enzymes, such as tryptophan hydroxylase and tyrosine hydroxylase. While Martineau (1988) [165] showed modest
improvements in about 30% of children, subsequent reviews concluded that there were few data to support the claim that vitamin B₆ improves developmental course [166, 167].

Fenfluramine

Although fenfluramine originally showed promise in the treatment of ASD and associated cognitive dysfunction [168], double-blind controlled trials did not confirm an improvement in cognitive function or a reduction in core autistic symptoms [169, 170]. However, much like naltrexone, fenfluramine may reduce hyperactivity and impulsivity commonly present in autistic disorder and other developmental disorders [171]. The potential changes in neurochemical regulation after long-term administration [170], which may represent neurotoxic effects [172], and potential for acquired cardiac valvular disease when coadministered with phenteramine, suggests that fenfluramine should no longer be used in ASD.

Secretin

A case series of three ASD patients who showed improvement in core symptoms after receiving the gastrointestinal hormone secretin [173], led to a series of studies of this substance as a possible treatment for ASD. The results have been disappointing, with all studies done so far showing the substance to be no more useful than placebo [174–182]. These studies, along with the negative studies that followed initial excitement following open-label studies of naltrexone and fenfluramine, point to the necessity of performing double-blind, placebo-controlled studies of any putative treatments to ensure safety and establish effectiveness (Table 21.5).

Summary and Future Considerations

Autism spectrum disorder has had a long and complex history that has paralleled the evolution of psychiatry. From the mysterious notion of children being reared by wolves [183], to profound maternal deprivation, to the contemporary notion of a genetic disorder with environmental influences, ASD has become a well-recognized and highly studied clinical condition starting in early childhood. Despite the long history of these disorders, their specific etiology and treatments for the underlying pathophysiology have yet to be discovered. However, some things remain constant:

(1) As one more carefully explores the “autism spectrum” it is apparent that ASD is a relatively common condition, with a prevalence of 2–3%.

Table 21.5  Summary of treatment principles.

<table>
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<tr>
<th>Psychosocial interventions</th>
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<tbody>
<tr>
<td>Education</td>
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<tr>
<td>Curricula that target communication:</td>
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<tr>
<td>– behavioral techniques</td>
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<tr>
<td>– structured milieu</td>
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<tr>
<td>– vocational training and placement</td>
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<tr>
<td>– other specialized interventions such as speech and language therapy, physical, and occupational therapy</td>
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<tr>
<th>Medical interventions</th>
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<tbody>
<tr>
<td>Cohesive doctor-patient relationship</td>
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<tr>
<td>Supportive measures for families coping with autistic disorder</td>
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<td>Behavioral treatment</td>
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<td>Pharmacotherapy to address problematic signs and symptoms</td>
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(2) The clinical picture of ASD remains complex with early onset and a range of severity from mild to severe with impairments in the domains of social, communicative, and flexible/adaptive behavior.

(3) The diagnosis can be made reliably and validly.

(4) Treatment is possible and leads to successful outcomes if it includes a coordinated, multidisciplinary approach that focuses on development of adaptive, social, and communicative functioning.

(5) Promising research is leading to a clearer picture of the ASD phenotype, and current studies are providing new insights into the neurobiology of this group of pervasive developmental disorders.

References

5. Kawamura Y, Takahashi O, Ishii T. Reevaluating the incidence of pervasive developmental disorders: impact of


