CHAPTER 76

# Developmental Disabilities

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## KEY CONCEPTS

1. Behavioral therapies, education, and pharmacologic treatment are complementary and should be integrated as part of a multimodal treatment approach in persons with developmental disabilities and concomitant behavioral issues.
2. Persons diagnosed with Down syndrome can be at increased risk for medical and psychiatric comorbidities.
3. When treating autism, objective and measurable outcome monitoring of psychoactive medication-responsive target behaviors is critical because of the variable response of individuals to medication therapy.
4. Many purported treatments for autism have limited or no evidence supporting their use. The use of such strategies should be discouraged, as many effective treatments exist.
5. Goals of treatment in persons with autism are to increase social interactions, improve verbal and nonverbal communication, and minimize the occurrence or impact of ritualistic repetitive behaviors and other related mood and behavior problems (e.g., overactivity, irritability, self-injury).
6. A structured approach to teaching, which focuses on increasing social communication and understanding and fosters integration with peers, is the treatment most highly correlated with improvement in persons with autism.
7. Although no medication has been shown to be universally effective, psychopharmacologic treatment in autism is effective and should be targeted at specific well-defined behavioral symptoms.
8. Rett's syndrome is characterized by the onset of developmental regression that occurs in four stages.

## INTRODUCTION

Developmental disabilities and mental retardation can be identified in childhood or adolescence. Current criteria for a diagnosis of mental retardation are based on deficiencies in intellectual and adaptive functioning with an onset prior to 18 years of age.[1,2] This diagnosis is made regardless of the presence or absence of concomitant medical or psychiatric disorders. In the case of mild mental retardation, deficiencies may not be initially apparent. Problems can be noted when the chronologic age of the child and the developmental milestones achieved by peers with similar backgrounds, cultures, and socioeconomic and psychosocial settings differ significantly.[1] These gaps widen as the individual ages.

1 Adaptive functioning deficits pose a number of challenges in treating those with a developmental disability (DD). This population can be four to five times more likely to experience mental health problems compared to the general population.[3] Until recently, little attention was given to this population and the need to evaluate them for psychiatric illnesses, leading to underrecognition of psychopathology. This oversight is a function of several factors, including limited, population-specific training for clinicians and a general lack of clinical contact with developmentally disabled individuals during training.[3] Additional barriers are patient-related deficits in expressive and receptive language, combined with a lack of mental health screening and diagnostic testing instruments specific to developmentally disabled adults.[3]

Those with developmental disabilities often have fewer social interactions and less integration into the community. In the absence of stimulation and interaction with peers that typically shapes behaviors in persons with normal intellect, a different set of coping skills can functionally evolve. An example is self-talk, which can represent such a coping mechanism in some persons with DD. This behavior can be misinterpreted by some as psychosis. Another potential problem for the clinician assessing persons with DD is a significant deficit between receptive language skills and expressive language skills. If not readily recognized, intellectual capabilities can be overestimated, and coping skills can be inadequate to deal with demands placed on the individual. This can result in anxiety-induced decompensation.[3]

In the general population, features of psychiatric illnesses are more readily identifiable, and the clinician is able to interview and evaluate the patient, as indicated. The term "diagnostic overshadowing" has been used to refer to clinician perception of behavioral problems thought to be secondary to mental retardation, which can actually be caused by a mental illness. Diagnostic overshadowing can therefore result in underestimating the clinical significance of the emotional and behavioral presentation as the deficits are inaccurately associated with a diagnosis of mental retardation.[3] This chapter will focus on three syndromes that are commonly seen in persons with developmental disabilities: Down syndrome, autistic disorder, and Rett's syndrome. In discussing these three syndromes, a broader perspective of issues encountered in persons with DD will be reviewed.

## CLINICAL PRESENTATION OF MENTAL RETARDATION[1]

**General Criteria**

- Either the diagnosis or onset of the disability occurs younger than 18 years old.
- When compared to peers, there is significant impairment in at least two areas of functioning.
- In the case of infants or very young children, formal testing might not be possible, and the assessment is based on clinical judgement.

**Problem areas can include the following:**

- The inability to progress in school with the same progress or mastery as others within the same social or cultural stratum.
- The individual can require support or adaptation in the work or vocational setting.
- The individual might not function well in less-structured environments and might not understand the rules of organized sports or games.
- The individual might lack an understanding of health or safety issues for self or others.

**Diagnostic Criteria**

- The level of mental retardation is determined by the intelligence quotient (IQ) score derived from formal testing.
- In cases of unspecified mental retardation, impairment is suspected by the clinician but cannot be measured.
- The most diagnosed level is borderline (IQ 71–84), which occurs in 7% of the general population.
- The next most frequently diagnosed category is mild (IQ 50–~70), which occurs in 3% of the general population.
- The prevalence of the other categories in the general population is significantly less:
- Moderate: IQ = 35–55; 0.4% of population
- Severe: IQ = 20–40; 0.1% of population
- Profound: IQ <20; unspecified

# DOWN'S SYNDROME

2 Down's syndrome (DS) is associated with common physical features and a wide range of health concerns, which include a number of developmental abnormalities. Congenital heart defects, seizures, orthopedic abnormalities, sensory defects, and disorders of the eye (cataracts, glaucoma), gastrointestinal tract, immune system, and thyroid disorders are all associated with DS. Persons diagnosed with DS also have a high probability of early onset Alzheimer's disease (AD).[4] This section will focus on DS and the comorbidities of Alzheimer's disease and leukemia.

Down's syndrome is the most frequently occurring chromosomal syndrome associated with mental retardation.[4] The first paper identifying persons with a common characteristic physical presentation of mental retardation, hypotonia, and abnormalities of the face, hands, and feet, was authored by John Langdon Down in 1866.[5] In 1959 chromosomal analysis identified the etiology to be the presence of an extra chromosome 21. Based on this finding, DS can also be referred to as trisomy 21 and represents one of the most studied conditions of chromosomal aneuploidy.[5]

## EPIDEMIOLOGY

Down's syndrome is a genetically mediated syndrome arising from trisomy of chromosome 21, as individuals have three copies of chromosome 21 rather than the normal two. The consequences of this variance are characteristic facial features, some degree of developmental disability, hypotonia, an increased risk for congenital heart disease, and early-onset Alzheimer's disease.[4] The incidence is estimated to be one in 600 to 1,000 live births.[5] Most of these individuals function in the mild to moderate range of mental retardation.[4]

## ETIOLOGY AND PATHOPHYSIOLOGY

Nondisjunction of chromosome 21 accounts for the majority of the mutations.[5] Chromosomes divide and separate in a process known as disjunction during meiotic division. Failure to fully separate at this stage can result in both chromosomes remaining in the same cell, resulting in an abnormal number of chromosomes on each strand. The origin of nondisjunction at chromosome 21 is almost exclusively maternal and strongly linked to maternal age.[5] Causative factors contributing to this nondisjunction of trisomy 21 have not been fully identified.

Increasing maternal age has been recognized to positively correlate with increased risk for DS. Although this has consistently been identified as a risk factor, the majority of DS births are to women younger than 35 years old.[4] The multifactorial nature of nondisjunction anomalies may be one explanation for this finding. Recent consideration has been given to both paternal age and grandparents' age as risk factors for DS. The possibility of paternally mediated nondisjunction has not been ruled out.[5] Evidence of a link has been inconclusive.[6,7] Risk factors from grandparents, particularly the age of the maternal grandmother, are under study. The particular aspect under investigation is whether an older mother passes an increased risk to her nonaffected daughter. To date, study results have not supported this concept.[8]

The time frame for maternal nondisjunction has been a topic of research interest. Use of maternal nutritional supplementation was investigated to determine if an association exists between use of nutritional supplementation during early pregnancy and the incidence of DS. The vulnerable period for nondisjunction may extend from 2 weeks preconception to implantation. This period of potentially heightened vulnerability was identified as the *periconceptual* period. A retrospective registry review using a case-control design was done to determine if there was a correlation between the use of nutritional supplements by women during the first month of pregnancy and DS. Ferrous sulfate (150–300 mg/day) and folic acid (approximately 6 mg/day) exerted a significant protective effect during the first gestational month. The majority of product use was concurrent.[9] The use of supplementation with the specific focus on DS prevention has not been undertaken as a practice standard.

## CLINICAL PRESENTATION AND DIAGNOSIS

Characteristic features make children with DS readily identifiable at birth.[4] The level of developmental disability is generally in the mild to moderate range.[2,4]

## CLINICAL PRESENTATION OF DOWN'S SYNDROME[2,4,10]

**General**

- DS is the most commonly diagnosed developmental disability.
- It results from an extra gene on chromosome 21.

**Diagnostic Features**

- The facial features can suggest DS, but an additional diagnostic evaluation is necessary.
- The degree of mental retardation ranges from mild to profound.
- Growth delays are common.
- Common physical characteristics:
  - Hypotonia can be evident at birth.
  - Facial features include flattened, broad facies with upslanted eye folds and a large, protruding tongue.
  - The palate can be narrow and the neck thick and broad.
  - Hands are characteristically short and broad.

**Other Clinical Concerns**

- There is an increased risk for congenital heart problems, and a cardiac evaluation is generally done shortly after birth with periodic followup.
- Congenital cataracts and hypothyroidism are common.
- Leukemia is often diagnosed in early childhood.
- By the third or fourth decade, features of Alzheimer's disease can present.

## TREATMENT

# Down's Syndrome

2 Treatment goals in DS are to identify comorbidities and provide effective nonpharmacologic and pharmacologic interventions to improve quality and duration of life. Medical screenings should assess for growth retardation, hypothyroidism, cardiac problems, sensory impairments to include hearing loss secondary to chronic otitis media, congenital cataracts or glaucoma, and gastrointestinal problems.[4,10,11] Guidelines for health supervision and anticipatory guidance in infants, children, and adolescents with DS are available through the American Academy of Pediatrics (AAP).[10] Routine screenings are also recommended by other medical groups throughout the course of life to address psychosocial changes, potential residential or vocational stressors, and the consequences of aging.

For the purpose of this chapter, the term *dual-diagnosis* refers to a developmentally disabled person with a comorbid psychiatric disorder.[12] Psychiatric comorbidities can occur in up to 25% of the DS population with depression the most common comorbidity.[4] The risk for depression is increased threefold in persons with DS compared to other intellectual disabilities.[13] 2 Recognition and treatment of affective disorders is often complicated by diagnostic overshadowing.[3,13] In persons with DS, verbal skills can limit self-report of mood. Changes in mood can be more accurately evaluated by increases in somatic complaints, sad facies, social withdrawal and isolation, and vegetative symptoms, including psychomotor retardation and changes in appetite and sleep. Depressed patients with DS are more likely to have hallucinations than other depressed patients. It is not clear whether the increase in hallucinations represents a prominent feature of depression in the DS population or if psychotic depression is more prevalent.[13]

2 The differential diagnosis for mood disorders should include an evaluation of thyroid function. Because clinical signs and symptoms of hypothyroidism can mimic some of the features of depression, thyroid function should be evaluated in those with DS.[13]

## NONPHARMACOLOGIC TREATMENTS

The use of social supports for both individuals with DS and the family is known to help develop the individual potential of each person with DS.[10] Early intervention programs do not change the basic genetic causation of the developmental disability, but social skills can be enhanced.[14]

In the treatment of psychiatric disorders, treatment modalities available to the general population also apply to those with DS. Nonpharmacotherapy options for depression include psychotherapy and electroconvulsive therapy (ECT), which can have applications in this population given the reported prevalence of hallucinations.[13] If expressive language skills are adequate, cognitive behavior therapy (CBT) can be used as a treatment option. This intervention focuses on learning new behaviors rather than the motivations for old ones. The theoretical framework for CBT can provide the basis for training in a variety of areas, such as social skills, anger management, and assertiveness.[15] Establishing rapport with the clinician is also significant, irrespective of verbal ability.[13]

As with any treatment regimen, adequate medication trials (appropriate dose and duration) with either an antidepressant or combination of an antidepressant and antipsychotic and ruling out comorbid medical conditions that could contribute to depression are needed. Psychotropic medication use in a large multicenter ECT study found in patients with psychotic depression 95% (101 of 106) had received inadequate antidepressant and antipsychotic dosing.[16] The use of vagus nerve stimulators for affective disorders has not been widely reported or studied.

## PHARMACOLOGIC TREATMENTS

In persons with DD, treatments to enhance cognitive abilities are not new. Vitamins, minerals, and other substances have been promoted to improve intellect. A systematic review of the literature regarding dietary supplements, drugs, and other supplements was done to evaluate these nontraditional treatment approaches. In addition to the agents used, the study design and evaluation measure were also reviewed. Positive results were not found, and the potential for adverse effects was raised because of the ready availability of some of the supplements, such as vitamins and minerals. Because of the heterogeneous methodologies, meta-analysis was not possible.[14]

Pharmacotherapy for the treatment of depression follows guidelines used in the general population. Antidepressants with serotonergic effects can be more efficacious, as altered serotonin levels have been found in persons with DS.[13] Amitriptyline, a tricyclic antidepressant with serotonergic activity, has been beneficial, and use of selective serotonin reuptake inhibitors (SSRIs) in accordance with existing guidelines is recommended.[13] Clinical trial use specific to this population has not been extensive, and most information has been based on small studies or case reports.

### DOWN'S SYNDROME AND ALZHEIMER'S DISEASE

Psychomotor retardation commonly seen in depression can be misinterpreted as symptoms of dementia. Apathy and loss of self-help skills are commonly reported with both depression and dementia.[17] Depressive symptoms can precede a diagnosis of AD.[13] Assessing changes in functionality and cognition are particularly problematic in this population, particularly in those with greater intellectual impairments. 2 Early studies did not identify the diagnostic criteria used for dementia of Alzheimer's type, a particularly important factor as DS is associated with an increase for early onset AD. A diagnosis of AD or dementia, Alzheimer's type, requires a decline in the individual's cognitive functioning from baseline capabilities. To help evaluate if criteria are met, the following are needed: baseline functioning information; reliable and sensitive test measures; functionality changes greater than explained by the general aging process; and progressive decline.[17] Identification of appropriate assessment scales has also been

problematic. The Dementia Scale for Mentally Retarded Persons was used as the primary outcome measure in a medication efficacy trial. It also provided secondary outcome measurement and assessment of cognition, neuropsychiatric features, adaptive behavior, and a global impression.[18]

### Pathophysiology

Neuropathologic changes of neuritic plaques and neurofibrillary tangles characterize AD, and the gene for amyloid-$\beta$ precursor protein is located on chromosome 21.[19] Neuropathic changes associated with AD are found in those with DS by age 40 years.[19] The increasing severity of DD has been theorized to have a significant impact on the incidence of Alzheimer's disease, but the results are inconclusive as the level of DD may limit evaluations.[17] The neurologic basis for DD may be one rationale for the increased vulnerability of this population. Neuronal development of the brain in those with DD is not as robust as the general population. A more thorough discussion of the pathophysiology of AD is beyond the scope of this chapter.

A population-based study found personality and behavior changes are primary features of the early stages of AD in adults with DS.[20] Changes in personality and behaviors include social withdrawal, apathy, and stubbornness. These changes do not meet the specific criteria needed for a diagnosis of AD because diagnostic criteria for AD include changes in short-term memory, language skills, and activities of daily living.[1,20] Mild cognitive impairment is considered a prodromal stage of AD in the general population. A longitudinal study of persons previously diagnosed with DS suggests personality and behavioral changes are key features in early stages of AD in this population as well.[20] However, information on the natural progression of cognitive changes in those with DS is limited.[18]

## TREATMENT

# Down's Syndrome and Alzheimer's Disease

Approaches to therapy for persons with DS and AD should include nonpharmacologic and pharmacologic interventions.

### NONPHARMACOLOGIC TREATMENTS

Traditionally, this has been a population with some level of supported living, whether still living in the family home or in a residential facility. As with the general population, treatment of AD for those with DS is multimodal and includes currently available treatments and supports in order to maintain functionality as long as possible. The plan of care should be adapted as needed.[18]

### PHARMACOLOGIC TREATMENTS

Pharmacologic treatments do not cure or stop the pathologic changes associated with AD. The goals of pharmacotherapy in persons with DS and AD are consistent with those for the general population: help slow cognitive function decline and help preserve the ability to assist in activities of daily living. The use of cholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) receptor antagonist in the DS population has received increased attention. Study sample size has been small, and research design has been problematic, limiting evidence-based research on medications used to help preserve cognitive functioning in the DD. Additional problems include rater bias, inclusion criteria, and applicability of rating instruments.[18]

There is, however, evidence to support the use of cholinesterase inhibitors to preserve global functioning and cognitive skills in persons with DS.[18,21,22] The bulk of the research for the DD has been with donepezil.[18,21] It is recommended pharmacotherapy be initiated at low doses and gradually titrated to help ameliorate adverse effects and increase compliance.[18] A 24-week, double-blind, placebo-controlled, parallel-group trial ($n = 30$) used the Dementia Scale for Mentally Retarded Persons as the primary outcome measure and the Severe Impairment Battery (SIB), Neuropsychiatric Inventory (NPI), and Adaptive Behavior Scale (ABS) as secondary measures. Dosing was 5 mg daily for the first 4 weeks, and 10 mg daily thereafter. Side effects included diarrhea, insomnia, fatigue, and nausea. A total of 27 patients completed the study. The authors concluded donepezil provided some limited benefit based on the finding of no clinical decline, but statistical significance was not reached for change in the outcome measures. Reductions in the Dementia Scale for Mentally Retarded Persons, SIB, and ABS did not reach statistical significance in the donepezil treatment group. Moreover, NPI scores improved in the placebo group (55% vs. 27.8%), although 50% ($n = 14$) of the donepezil treatment group showed mean Dementia Scale for Mentally Retarded Persons score improvement compared to 31% ($n = 13$) of those untreated. Nonsignificant findings might have been a function of small sample size. Use of donepezil was associated with improvement in cognitive impairment.[23]

The use of rivastigmine, galantamine, or memantine in the DD has not been studied as extensively as donepezil. An assessment of the efficacy of rivastigmine for dementia in AD in the general population and the DS population was undertaken. Baseline functionality evaluations with the Dementia Scale for Mentally Retarded Persons, NPI, and ABS were done. Scores for the placebo group ($n = 13$)[23] were based on an untreated group from a previous study. The rivastigmine-treated group ($n = 17$) received 1.5 mg twice daily at initiation and were titrated up to a total daily dose of 12 mg over 8 weeks. Findings were not statistically significant for any of the measures. Scores for both groups declined on the Dementia Scale for Mentally Retarded Persons, less so for the rivastigmine group (7.8% vs. 10.7%). Adaptive behavioral changes, as measured by the ABS, were greater in the placebo group (9.1% vs. 7.1%). The authors reported improved NPI scores for both groups (11% with rivastigmine vs. 55% with placebo). Rivastigmine-associated adverse effects included gastrointestinal upset (diarrhea, nausea, vomiting), fatigue, and insomnia. Failure to achieve statistical significance can be the result of the small sample size.[22] The majority of adverse effects reported with cholinesterase inhibitors were cholinergic system mediated, including nausea, vomiting, diarrhea, insomnia, and fatigue.[18]

2 Medical comorbidities are also of concern in the DS population. Either the preexisting medical condition or pharmacotherapy can contraindicate use of cholinesterase inhibitors. Cholinesterase inhibitors are contraindicated with sick sinus syndrome, additional cardiac conduction disturbances, a history of peptic ulcers, and hepatic and/or renal impairment.[18] Concomitant drug therapy cannot be ignored because of the potential for relative and absolute contraindications.

Pharmacokinetic variances seen with donepezil in persons with DS have not been fully explained. A small case study ($n = 14$) found significantly higher plasma concentrations in DS individuals compared to healthy volunteers. A dose in the range of 2.5 mg daily may be appropriate, with an increase to 5 mg if needed, with careful monitoring. No relationship between level of DD and adverse reactions was found.[24]

2 Monitoring for new onset seizure activity and adding appropriate pharmacotherapy with anticonvulsants is needed because of the prevalence of seizure disorders for both AD and DS. Advanced AD can constitute a risk factor for new onset seizure activity,[25] and an association between DS and AD has been shown.[17,18] For those with AD, 10% have seizures. An additional 10% have myoclonal episodes. This occurs more frequently than generalized tonic-clonic and partial seizures. An earlier onset of AD is associated with an increased likelihood of seizure activity. In the DS population, seizure activity increases with age.[25]

Overall, seizure frequency in the DS population averages approximately 8%. Distribution is bimodal. The first cluster appears prior to 1 year of age and is predominately infantile spasms and tonic-clonic with myoclonus. The second cluster occurs in patients who are 20 to 29 years of age (third decade) and is primarily partial and tonic-clonic seizure activity. Seizure patterns in the DS population, in order of prevalence, are partial (47%), infantile spasms (32%), followed by generalized tonic-clonic (21%).[25] Specific treatment guidelines for those with DS and comorbid seizure activity have not been developed. Currently available findings have focused on comparisons of seizures, electroencephalograph (EEG) results, and the impact on functional cognition-related status or changes.[25]

## Evaluation of Therapeutic Outcomes

Research on the use of cholinesterase inhibitors and memantine has been limited in the DD population. Therapeutic goals for persons with DS and AD are to maintain the quality of life as closely to baseline as possible for as long as possible. Because of the early onset of AD, baseline functioning levels should be established prior to the onset, generally in the third or fourth decade. This can be particularly important in those individuals without expressive language skills. Followup evaluations should be recommended annually. If cholinesterase inhibitors are used, evaluations every 2 to 4 months (after achieving a maintenance dose) are recommended to monitor for effectiveness if the anticipated positive gains have not been observed.[18]

Monitoring for potential medication-related side effects is also recommended. The most commonly reported side effects were gastrointestinal-related effects (diarrhea, nausea, vomiting), insomnia, and fatigue. The onset of increased bowel incontinence can represent a medication effect rather than cognitive decline.

### CLINICAL CONTROVERSY

A diagnosis of trisomy 21 can predispose an individual to early onset AD. The length of time to use cholinesterase inhibitors in persons with DS is controversial because of the lack of availability of baseline information and standardized assessment instruments that limit generalization of treatment guidelines. In addition, knowledge of the natural course of cognitive decline because of AD in the DS population is limited. Further study is needed to determine the long-term efficacy of cholinesterase inhibitors and NMDA receptor antagonists in the treatment of AD.[18]

## DOWN'S SYNDROME AND THE IMMUNE SYSTEM

2 Neuropathologic changes are not the only abnormalities associated with DS. Two forms of leukemia are more commonly encountered in DS children: acute leukemia (AL) and transient leukemia. Compared to the non-DS pediatric population (identified as 4 years old or younger), children with DS have a higher incidence of developing AL, with acute myelogenous leukemia (AML) comprising the majority of cases. The specific form of AML is acute megakaryoblastic leukemia or AML-M7. The incidence of this disorder in DS has been identified as high as 500 times greater than in the general pediatric population.[26] For transient leukemia, the prevalence in DS neonates has been estimated to be 10% to 20%. It can spontaneously remit within 3 months and clinically cannot be differentiated from AL. Within 1 to 3 years following spontaneous remission of transient leukemia, however, 25% of this population will develop AL.[26]

The link between the genetic mutation on chromosome 21 and the increased prevalence of leukemia in DS children has been explored. The theoretical explanation with the most support is the presence of a gene on chromosome 21, which predisposes the individual to blood cell formation abnormalities.[27]

Although the DS population has an increased risk for the development of leukemia, survival rates are also higher than in the normal pediatric population.[28] Children with DS do, however, experience more treatment-related toxicities. Several retrospective studies have analyzed treatment protocols. At this time, no specific protocols addressing dose intensity and treatment-related toxicities are available.[28] The Nordic Society of Paediatric Haematology and Oncology acute myeloid leukemia protocols contained data on 56 DS children. Adverse effects were identified in 53% (8 of 15) of patients given a more dose-intensive protocol compared to 17% (7 of 41) given the less dose-intensive protocol. Specifically, dose reductions were made for 52% (29 of 56) of the patients on scheduled doses of anthracycline (75%) and cytarabine (67%).[28]

In another retrospective review of 34 DS children diagnosed with AML, remission rates for those treated with low-dose protocols, which included cytarabine, found 83.3% (15 of 18) achieved complete remission compared to 93.7% (15 of 16) in the standard-dose protocol. Between-group toxicity comparison was not a component of this study, however.[29]

### Evaluation of Therapeutic Outcomes

Therapeutic goals for those with DS and leukemia are to promptly diagnose the condition, optimize treatment outcomes, and improve the quality of life. Guidelines for health supervision, monitoring, and anticipatory guidance in infants, children, and adolescents with DS are available through the American Academy of Pediatrics (AAP).[10] Older persons with DS have an increased risk for a variety of medical problems including hypo- and hyperthyroidism, leukemia, and seizures.[4]

## CONCLUSIONS

Down's syndrome is the most common chromosomal cause of mental retardation.[4] The well-known list of phenotypic variations and minor anomalies are recognizable at birth, and congenital abnormalities can increase the mortality rate compared to the general population. Treatment options used in the general population are also applicable in the DS population with the goal of resolution of medication-responsive target behaviors.

# AUTISTIC DISORDER

Autism is a behaviorally defined pervasive developmental disorder. Other pervasive developmental disorders include Rett's disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified.[1] The pervasive developmental disorders are characterized by severe and sustained impairments in three behavioral domains: (1) reciprocal social interaction (withdrawal or lack of interest in peers), (2) language and communication skills (limitations in the use of speech and nonverbal skills), and (3) range of interests and activities (abnormal preoccupations, stereotyped mannerisms). Autism is not a disease but a syndrome with multiple possible etiologies. The onset is typically younger than 3 years of age, and is usually, but not necessarily, associated with some degree of mental retardation.[1,30] The core features of autism are deficits in language usage, impairments in social reciprocity, and behavioral rigidity. Autism was first described by Leo Kanner in 1943, and has been historically described as early infantile autism, childhood autism, and Kanner's autism.[31]

## EPIDEMIOLOGY

There has been a recent sharp increase in the reported prevalence of autism (556% in pediatric prevalence between 1991 and 1997), surpassing that of spina bifida, cancer, or DS.[32,33] It is suggested that the increased reported prevalence is primarily caused by changing and broadening diagnostic criteria and an increased index of suspicion, rather than by an actual increased incidence.[32,33] As autism is behaviorally defined, the diagnostic boundaries are not always clear. Some behaviors (such as stereotypies) seen in persons with autism can also be seen in nonautistic individuals and can be associated with age-appropriate behavior. There is a significant impact of developmental level on the expression of symptoms of autism, resulting in a lack of homogeneity in clinical expression of the condition.[33] Although early studies reported prevalence rates of 2 to 5 per 10,000 for autism, and recent reports have suggested rates of up to 60 per 10,000,[31] a more realistic rate is considered to be 10 per 10,000.[34] The onset of autism is prior to 3 years of age, however, the syndrome may not be recognized until later. Autism is four to five times more prevalent in males, and females with autism are more likely to have more severe DD associated.[31] No studies have clearly demonstrated an association between autism and socioeconomic status of the parent; however, there has been a common myth that autism was correlated with higher socioeconomic strata.[31]

### CLINICAL CONTROVERSY

It has been postulated that thimerosal, a preservative used in many vaccines, which contains ethyl mercury, could be causally linked to neurodevelopmental disorders such as autism. Population-based epidemiologic and cohort studies have found no link between thimerosal-containing vaccines and the development of autism.[35,36] Further concerns were posed specific to a postulated link between the measles/mumps/rubella vaccine and autism. A review of the evidence did not support this hypothesis; however, it continues to be an issue with many advocates for persons with autism.[35–38]

## ETIOLOGY AND PATHOPHYSIOLOGY

Early models of causality for autism involved theories of faulty parenting.[30] However, it has since become clear that autism has a biologic basis, with multiple interacting genetic factors serving as the primary cause for autism.[32] Current research focuses on genetics and neuropathology. Environmental exposure such as toxic chemical exposure, teratogens, perinatal insults, and prenatal infections account for only a few cases. Immunization with measles/mumps/rubella vaccine has not been confirmed by evidence to be causative.[32] Autism can occur concomitantly with epilepsy and may be associated with the single gene defect conditions called fragile X syndrome, neurofibromatosis, and tuberous sclerosis.[30] Currently, cytogenic conditions, diagnosable medical conditions, single gene defects, and other rare diseases account for less than 10% to 25% of cases of autism.[30,32]

Although the single genetic mutation or variant leading to autism has yet to be identified, autism appears to be a highly heritable disorder.[32,39] Siblings of affected children have a 50 to 100 times greater risk of having autism (2%–8%) than those in the general population.[32,39] As autism does not follow a simple Mendelian mode of transmission (i.e., recessive or dominant transmission), a commonly accepted model involves polygenic transmission involving five to ten genes that interact to produce the disorder.[39] Results from twin studies and family studies suggest that the social and cognitive deficits seen with this syndrome are part of a larger phenotype of autism. X-linkage transmission (male to male) has been ruled out as a primary mechanism for transmission of the syndrome.[32]

Postmortem studies have indicated a number of brain abnormalities in individuals with autism. These include a decreased number of neurons and reduced dendritic arborization in the limbic system (including amygdala, hippocampus, septum, and anterior cingulate).[30,40,41] Studies are limited by small sample size and lack of closely matched control groups. Abnormalities in the limbic system are of interest because of the impairments in social reciprocal function seen in persons with autism; the limbic system includes the "social brain" described by Brothers.[41] There have also been reports of decreased numbers of Purkinje cells in the cerebellum.[30,40] This abnormality has been postulated to lead to disinhibition of the cerebellar deep nuclei and the subsequent hyperexcitability of the thalamus and cerebral cortex.[41] Structural magnetic resonance imaging findings have not been correlated with the neuropathologic findings in autism. However, the findings have substantiated the increased brain volume (2%–10% increase) observed in autism cases.[40] The neuropathologic changes noted in persons with autism are suggested to be of prenatal origin, primarily in the first 6 months of gestation.[40]

There are reported decreases in the nicotinic receptor binding in the cholinergic system as well as decreased function in the $\gamma$-aminobutyric acid (GABA)ergic system in persons with autism.[40] Nicotine enhances several cognitive and psychomotor behaviors, and opens the possibility of therapeutic intervention via cholinergic receptor modulation.[40] Approximately one-third of children with autism have elevated peripheral platelet concentrations of the neurotransmitter serotonin. Studies of dopamine and catecholamine metabolites have failed to consistently show abnormalities of this neurotransmitter system. The dopamine system is of research interest because of the high prevalence of stereotypic movements in persons with autism.

## CLINICAL PRESENTATION AND DIAGNOSIS

The differential diagnostic features of autism and nonautistic pervasive developmental disorders are listed in Table 76–1. A multiple step process has been suggested for a structured approach to differential diagnosis of suspected autistic disorder, beginning with a determination of intellectual function and level of language development. Next, consideration must be given to the child's behavior as it relates to the chronologic age, mental age, and language age. It is important to identify any relevant medical conditions, and consider the presence of any relevant psychosocial factors.[31]

Persons with autistic disorder are typically normal in physical appearance. There are minor physical abnormalities that are not uncommon in persons with autism, such as ear malformations, delayed development of hand dominance, and abnormal dermatoglyphics/fingerprints.[31] There is a significant comorbid occurrence of seizure disorder, with up to 25% of autistic individuals having a seizure disorder by adulthood. Those with comorbid seizure disorders can have greater impairment in intellectual function.[1] There is also a common association with fragile X syndrome and tuberous sclerosis.[1,31]

The cardinal features of autistic disorder are gross and sustained impairment of reciprocal social interaction, sustained abnormalities in verbal and nonverbal communication skills, and restricted, repetitive, and stereotypical patterns of behavior, interests, and activities.[1,31] In most (estimated at 75%) cases, there is an associated diagnosis of mental retardation, ranging from mild to profound. Approximately 30% of persons with autism function in the mild to moderate range of mental retardation, whereas 45% to 50% are severely to profoundly mentally retarded.[31] Epidemiologic data suggest that the risk for development of autistic disorder increases as the IQ decreases.[31] Although there can commonly be abnormalities in the development

**TABLE 76-1** Differential Diagnostic Features of Autism and Nonautistic Pervasive Developmental Disorders

| Feature | Autistic Disorder | Asperger's Syndrome | Classical Rett's Syndrome | Childhood Disintegrative Disorder | Pervasive Developmental Disorder–NOS |
|---|---|---|---|---|---|
| Age at recognition (months) | 0–36 | Usually >36 | 5–30 | >24 | Variable |
| Sex ratio | M > F | M > F | F (?M) | M > F | M > F |
| Loss of skills after initial mastery | Variable | Usually not | Marked | Marked | Usually not |
| Social skills | Very poor | Poor | Varies with age | Very poor | Variable |
| Communication skills | Usually poor | Fair | Very poor | Very poor | Fair to good |
| Circumscribed interests | Variable (mechanical) | Marked (facts) | NA | NA | Variable |
| Family history of similar problems | Sometimes | Frequent | Not usually | No | Unknown |
| Seizure disorder | Common | Uncommon | Frequent | Common | Uncommon |
| Head growth decelerates | No | No | Yes | No | No |
| IQ range | Severe MR to normal | Mild MR to normal | Severe MR | Severe MR | Severe MR to normal |
| Outcome | Poor to good | Fair to good | Very poor | Very poor | Fair to good |

F, female; IQ, intelligence quotient; M, male; MR, mental retardation; NA, not applicable; NOS, not otherwise specified.
*Data from American Psychiatric Association,[1] Chawarska and Volkmar,[43] Flipek et al.,[44] and Volkmar and Cohen.[115]*

of cognitive skills in most persons with autistic disorder, unusual abilities can be noted in some cases, called splinter functions or islets of precocity. The most significant of these are evidenced in the autistic savant, in which a person with autistic disorder can have precocity in mathematic calculations, art, music, or rote memory.[1,31]

Autistic disorder is typically diagnosed prior to the age of 3 years. In many instances, parents note that they have been concerned about the child's lack of interest in social interactions since birth or shortly afterward.[1] Studies have shown that a diagnosis of autism can be reliably made between ages 2 and 3 years.[42] Features that identify children in infancy with autism early in development include lack of a social smile, lack of facial expression, poor attention, and impaired social interaction. Further, by 2 years of age, traits such as social indifference, preference for isolation, lack of making eye contact, lack of emotional expression, less looking at others, less pointing, and less showing of objects identify children for the possible need for followup.[42] Table 76–2 contrasts symptoms that assist in differentiating infants and toddlers with autism from typical and developmentally delayed peers.[1,43]

Early identification of at-risk children leading to diagnosis is desired so that appropriate structured multidisciplinary interventions can occur. Behaviors suggesting the need for a developmental evaluation include lack of babbling, pointing, or other gestures by 12 months, no single-word language development by 16 months, no two-word language development by 24 months of age, and loss of previously held language or social skills at any age.[44] Such early intervention improves outcomes by enhancing functional ability in later life, and further, diagnosis with genetic screening can assist the parents in family planning.[42] It is difficult to determine if autism is present in persons with severe to profound mental retardation. A diagnosis of autism is made in such cases when there are qualitative deficits in social and communicative skills and the specific behaviors characteristic of autistic disorder are present.[1] A central difference is that persons with mental retardation alone typically relate to adults in a manner consistent with their mental age, use their language to communicate with others, and present with a relatively even profile of impairments without splinter functions.[31]

Screening tools, such as the Parent's Evaluation of Developmental Status can assist clinicians in the early detection and diagnosis of autism. The Checklist for Autism in Toddlers and the Pervasive Developmental Disorders Screening Test–Stage I are specific for autism and are often used to assist in the diagnostic process.[45] The Childhood Autism Rating Scale (CARS) was initially designed as a diagnostic instrument for young children to be completed by trained clinicians following behavioral observations. It has also been used with adolescents and adults, and as an informant-based assessment tool. The CARS is widely used for screening and diagnostic purposes; however, it is not designed to measure behavioral changes

**TABLE 76-2** Symptoms Differentiating Infants and Toddlers with Autism from Normal and Nonautistic Developmentally Delayed Peers

| | Social Interactions | Communication | Stereotypical Behaviors and Repetitive Patterns |
|---|---|---|---|
| First-year characteristics in persons with autism | Limited ability to anticipate being picked up<br>Low frequency of looking at people<br>Little interest in interactive games<br>Little affection toward familiar people<br>Content to be alone | Poor response to name<br>Infrequent looking at objects held by others | Excessive mouthing<br>Aversion to social touch |
| Second- and third-year characteristics in persons with autism | Abnormal eye contact<br>Limited social referencing<br>Limited interest in other children<br>Limited social smile<br>Low frequency of looking at people<br>Limited range of facial expressions<br>Limited sharing of affect/enjoyment<br>Limited interest in interactive games<br>Limited functional play<br>No pretend play<br>Limited motor imitation | Low frequency of verbal or nonverbal communication<br>Failure to share interest (e.g., through pointing, giving, and showing)<br>Poor response to name<br>Failure to respond to communicative gestures (e.g., pointing, giving, and showing)<br>Use of other's body as a tool<br>Unusual vocalizations | Hand and finger mannerisms<br>Inappropriate use of objects<br>Repetitive interests/play<br>Unusual sensory behaviors (hyper- or hyposensitivity to sounds, textures, taste, visual stimuli) |

*Data from American Psychiatric Association[1] and Chawarska and Volkmar.[43]*

**TABLE 76-3** Medical Screening for Individuals with Autism

| Parameter | Rationale |
|---|---|
| Medical and developmental history | Confirm diagnosis, identify underlying cause, assess strengths and weaknesses, identify comorbidities, measure head circumference, identify resources needed |
| Wood's light exam | Identify depigmented macules associated with tuberous sclerosis |
| Hearing and vision testing | Profound hearing loss can illicit symptoms mimicking autism (receptive language deficits); most are normal |
| Lead and heavy metal testing | Perform if there is a history of cyclic vomiting, early onset seizures, dysmorphic features, presence of mental retardation or developmental delays |
| Genetic testing for karyotype and fragile X, Rett's syndrome | Benefits family for genetic counseling purposes |
| Test for inborn errors of metabolism/metabolic testing | Indicated in those with a history of lethargy, cyclic vomiting, early seizures, dysmorphic or coarse facial features, mental retardation |
| CBC, thyroid function testing | CBC if anemia suspected; thyroid function tests to rule out baseline thyroid abnormality that can affect mood/activity level |
| EEG | Evaluate neurologic findings that cannot be explained by the diagnosis of autism alone or in the presence of developmental regression |
| Neuroimaging | Evaluate neurologic findings that cannot be explained by the diagnosis of autism alone–very low prevalence of focal lesions seen in persons with autism |

CBC, complete blood count; EEG, electroencephalograph.
*Data from Flipek et al.,[44] and Prater and Zylstra.[45]*

because of a lack of sensitivity to change of certain scale items.[46] Adaptive behavior deficits are seen in the majority of persons with autism. A commonly used tool for the purpose of characterizing the presence and severity of these deficits is the Vineland Adaptive Behavior Scales.[47] This is a semistructured informant interview that assesses an individual's daily function, which can be completed by caregivers, family, or teachers. This scale is most useful for diagnostic and prognostic purposes and is not likely to reflect changes in short-term treatment interventions.

As there are no definitive biologic markers for identifying individuals with autism a number of medical evaluations should occur, to assist in distinguishing the diagnosis as autism, and ruling out other possibilities. Table 76–3 delineates the parameters to be considered in a medical evaluation for persons suspected of having autism, along with the rationale for the assessment.

Seventy-five percent of individuals with autism have some degree of mental retardation. Those with IQs above 70 and who use communicative language by ages 5 to 7 have the best prognoses.[31] Conversely, low IQ scores and failure to develop communicative language by age 5 years correlate with a poorer long-term prognosis.[45] Outcome studies in persons with autism correlate IQ, particularly verbal IQ, with ability to be employed and live independently.[42] Learning disabilities are a risk factor for behavioral problems, and 41% of children with mild, moderate, or severe learning difficulties have a severe emotional behavioral disturbance.[42] Studies indicate that high IQ children with autism can make positive changes in communication and social domains over time. The areas less likely to improve are those related to ritualistic and repetitive behaviors.[31] Approximately two-thirds of adults with autism require supervision and supports for living, 1% to 2% are able to live independently with no supports, and 5% to 20% achieve near normal functional status.[31]

## CLINICAL PRESENTATION OF AUTISTIC DISORDER[1,43,44]

**General**

- Symptoms must be present before age 3 years.
- Delays or abnormalities in six or more of the symptoms below with at least two impairments in social interactions and one each in communication and restricted interests or repetitive behaviors.
  - Significant impairment in nonverbal communications
  - Unable to develop peer relationships
  - Lack of spontaneous interactions with people or the environment
  - Developmental delays in communication
  - Inability to use expressive language appropriate to developmental level
  - Lack of developmentally appropriate play
  - Stereotypical or nonfunctional ritualistic behavior
  - Inability to tolerate change
  - Stereotypic or repetitive, nonfunctional motor movements
  - Limited scope of play or interest

# TREATMENT

## Autistic Disorder

3 The treatment plan should address (1) establishing realistic goals for educational efforts, (2) identifying behavioral target symptoms for intervention, (3) prioritizing target symptoms and comorbid conditions for intervention, (4) using specific methods of outcome monitoring of functional domains (behavioral, adaptive skills, academic skills, social interaction skills, communication skills), and (5) monitoring for efficacy and potential adverse effects of medication (if used). An effective, well-designed, multimodal treatment plan that is consistently executed can positively shape the autistic individual's interaction with the environment and improve the quality of life of the patient and their family.

### NONPHARMACOLOGIC THERAPY

4 After a thorough diagnostic evaluation, treatment planning for the individual with autism is critical to assure consistency and efficacy of interventions. With the often severe nature of the behavioral and adaptive problems, it is not surprising that many potential treatment modalities have been proposed for persons with autism. The two treatment approaches for autism with the most significant body of evidence-based support and clinical consensus are behavioral/psychoeducational therapies and psychoactive medication intervention.[48] Although there have been considerable advances in early intervention strategies, research regarding the comparative efficacy of the various interventions (education, psychosocial, psychopharmacology) is lacking. All stakeholders (family, educators, and clinical professionals) should be involved in the treatment planning process. Treatment decisions should be evidence based and focused on the specific identified needs of the individual. Overreliance on patient verbal reporting for assessment of psychopathology should be avoided because of the potential for communication deficits. A multifaceted approach to information gathering should include direct observation, as well as interviews with parents/family, caregivers, teachers, and review of the medical record (including any behavioral rating scale information).[3]

Educational services are a central aspect of psychosocial treatment services for individuals with autism. 5 Available evidence suggests that appropriately designed, consistently implemented educational services positively impact the acquisition of social, communicative, self-care, and cognitive skills, each of which facilitates the person's long-term success. Federal law 94–142 mandates the provision of appropriate educational planning for all children in the United States and confers certain rights to parents.[49] Ancillary services, such as occupational therapy, physical therapy, and speech pathology, are often required as integral aspects of an overall educational plan. 6 Because of the pervasive need for sameness in routine, ongoing and consistent year-round educational programming is more effective than intermittent, episodic interventions. Training of teachers and parents in appropriate behavioral management techniques, and collaboration/consistency among these groups in management approaches is essential to program success.[49] Researchers have referred to communication as a pivotal behavior that can influence other features of autism. The inference is that effective language training can lead to generalized improvements in social skills, repetitive behaviors, and other nonspecific behavioral problems such as noncompliance, self-injury, and aggression.[48]

Behavior modification procedures have been demonstrated to decrease inappropriate behaviors and foster social interaction and language acquisition. Behavior modification involves principles such as structuring the environment, providing consistent responses to behaviors, rewarding positive behaviors, not rewarding negative behaviors (negative reinforcement), application of an adverse stimulus to deter an unwanted response (punishment), and reinforcing closer and closer approximations to the desired behavior (shaping).[45]

Parents can solicit additional ancillary treatment providers outside of the school and team setting. It is important that these service providers integrate their actions with those of the team, to provide for a consistent approach to treatment across all multidisciplinary team members.[49]

## PHARMACOLOGIC THERAPY

In addition to the core symptoms of autism, many persons with this disorder exhibit other significant problem behaviors, such as self-injury, aggression toward others, and severe tantrums in response to routine demands. These behavior issues can interfere with day to day activities and are challenging for families, caregivers, and educators to effectively manage.[50] Current research on the neurobiologic basis of autism is centered on the serotonin, peptidergic, dopaminergic, and noradrenergic systems. Despite limited evidence-based support, psychoactive medications have been widely used to help diminish the frequency and intensity of these behaviors. 7 It is important that clinicians identify and carefully monitor specific target symptoms response to avoid the practice of overprescribing psychoactive medications. Only risperidone is currently Food and Drug Administration (FDA) approved to treat the behavioral symptoms associated with autism.[51] However, off-label use of FDA-approved medications (i.e., use of an approved drug for an unapproved use) is an acceptable clinical practice when there is evidence-based support for the use of the medication, and informed consent is obtained.

Most research on pharmacotherapy in autism has been directed at management of behavioral symptoms. Most studies of psychopharmacologic interventions in persons with autism have been limited by problems in experimental design, sample size, loose or poorly defined diagnostic criteria, and many clinical outcomes have been limited in duration or of dubious significance.[52] Psychopharmacologic medications to date have not been identified which alter the core symptoms of autism, and they are not curative. 5 7 Nevertheless, such medications can be helpful, as part of a multifaceted treatment program, in minimizing behavioral and/or psychiatric problems that interfere with educational interventions or in ameliorating symptoms that limit social interaction.[45,53] Dopamine-blocking agents and serotonin reuptake inhibitors have clinically significant effects on some aspects of the core symptoms of autism when examined in randomized controlled clinical trials.[48] This is consistent with the majority of the existing neurobiologic evidence that points toward aberrant behaviors in autism being associated with dysregulated dopamine and serotonin systems in the brain.[48]

Prevalence studies of psychoactive medication use in this population have consistently reported higher rates of medication use in persons living in more restricted living arrangements (institutions or sheltered living environments), older age, more severe autism, and more severe mental retardation.[53,54] A survey of psychoactive medication use in this population in 1993 by Aman and colleagues found that 34% of the sample was prescribed some psychoactive agent, with antipsychotic agents being the most prevalent. Other medications cited in this seminal analysis were psychostimulants, sedative hypnotics, and antidepressants, in descending frequency of use.[55] In a followup study of 3,228 families involved in the Autism Society of North Carolina in 2001, the largest study of psychoactive medication use in this population to date, changes in the patterns of use of psychoactive medications were reported. The rate of antidepressant use (21.4%) reflected a 250% increase compared to the 1993 evaluation, reflecting a shift in practice for use of antidepressants to treat depressive symptoms as well as perseverative, stereotypic, and aggressive behaviors.[53] The use of atypical antipsychotics in this study (16.8% of patients) comprised 85% of all antipsychotic agents used, in part because of the presumed lower risk of extrapyramidal symptoms and tardive dyskinesia with the atypical agents.[52,53] This shift in medication selection also reflects emerging patterns in neurobiologic research findings as discussed above.

There is a significant body of evidence to support the idea that the typical or conventional antipsychotic agents are not well tolerated by many persons with autism, due primarily to medication-induced extrapyramidal movements, including akathisia.[56–58] Dopamine blockade results in neuromotor adverse effects, including dystonia, pseudo-parkinsonism, and tremors.[39] The atypical antipsychotic agents are less likely to illicit extrapyramidal side effects than the typicals but have been implicated in weight gain and sedation in some persons with autism. Of the atypical antipsychotic agents, risperidone and olanzapine currently have the most significant evidence-based support for use in treating behavioral problems associated with autism. Risperidone is FDA approved for treatment of aggression, self-injurious behavior, temper tantrums, and mood changes associated with autism in children and adolescents.[48,50,58–65] Case reports support the use of quetiapine, ziprasidone, and clozapine in attenuating behavioral symptoms such as self-injury, aggression, agitation, and repetitive behaviors.[66–72] Most published studies indicate improvements in nonspecific behavioral concerns such as aggression, self-injurious behavior, irritability, and anxiety.[56,58] However, few studies with atypical antipsychotics show a sustained statistically significant impact on any core features of autism, such as deficits in language usage, impairments in social reciprocity, or behavioral rigidity.[48]

Serotonin modulates sensory perception, motor function, memory, and sleep. Many of these functions are dysregulated in persons with autism.[73] One theory posits possible deficits in the serotonin transporter gene in persons with autism; however, data are conflicting in support of this.[74] Serotonin reuptake inhibitors have been used to treat stereotypies, ritualistic behavior, aggression to self and others, repetitive behaviors, and over-adherence to routines.[73,75] The increase in the use of serotonin reuptake inhibitors to address symptoms of autism corresponds with the emerging efficacy data, as well as the perception of increased safety compared to conventional

tricyclic antidepressants. Fluoxetine, sertraline, and fluvoxamine are the selective serotonin reuptake inhibitors with the most published evidence supporting their use; however, reports on the use of other serotonin reuptake inhibitors also exist.[73]

Mood stabilizing antiepileptic drugs such as divalproex are commonly used to treat bipolar disorder, and there has been much interest in their use in persons with autism to modulate impulsivity and aggression.[76] A small open label, retrospective pilot study of patients ($n$ = 14) aged 5 to 40 years with pervasive developmental disorder (PDD) reported that divalproex improved affective instability, impulsivity, and aggression.[75] Controlled clinical trials are needed to replicate and validate the early findings, however persons with autism who have affective instability, impulsivity, and aggression, especially with a comorbid seizure disorder or EEG abnormality, can benefit from valproate therapy.[76] The evidence for the use of lamotrigine is limited, with mixed efficacy results in this population. Lithium has been shown to be effective in treating mood lability in some persons with autism.[77] However, lithium has a narrow therapeutic index and requires significant clinical monitoring, and the mood stabilizing antiepileptic drugs are considered to be an effective and safer option.

The efficacy of psychostimulants can be limited to those with autism and comorbid attention-deficit disorder (ADD). The psychostimulants methylphenidate and dextroamphetamine have been studied in persons with autism to address hyperactivity, impulsivity, and inattention. Dextroamphetamine has not been clearly demonstrated to provide clinical improvements, and the side effects of increased stereotypy and irritability in some patients were problematic.[75] Methylphenidate has been demonstrated, in a small number of controlled trials, in doses of 0.3 to 0.6 mg/kg/day, to provide varying degrees of improvement in target symptoms.[75,78,79] The side effects reported were similar to those reported with dextroamphetamine, as well as dysphoria, social withdrawal, and crying. Anorexia, increased aggression, and tic disorder have also been reported with methylphenidate.[75]

The $\alpha_2$-agonists, clonidine and guanfacine, have been widely used to treat hyperactivity and agitation in persons with autism. As with many psychoactive medications used in this population, there is a lack of large-scale, rigorous, methodologically sound studies.[75] Sedation and hypotension were commonly observed adverse effects. $\beta$-Blockers (primarily propranolol) have been used for symptoms of aggression and impulsivity. Similar to the $\alpha_2$-agonists, published literature is limited to case reports.

Based on the hypothesis that a dysregulated endogenous opioid system can underlie the presentation of some behavioral symptoms of autism, naltrexone, an opioid antagonist, has been used to target extreme self-injurious behaviors in this population. Naltrexone doses ranged from 0.5 to 2 mg/kg/day, and the most predominant adverse effect was transient sedation.[80] Animal studies have demonstrated that low doses of $\beta$-endorphins increase social approach behavior in rats, whereas high doses decrease such behaviors.[81] Open-label studies in human subjects suggest that there can be therapeutic benefit, based on a theory of a dysregulated opioid system.

Case reports also suggest that naltrexone can improve hyperactivity, agitation, irritability, tantrums, social withdrawal, and stereotypic behaviors.[80] Subsequent controlled studies have shown some efficacy on self-injurious behaviors, minimal to no efficacy for other symptoms of autism (social deficits, stereotypies), and minimal adverse effects.[75,82] Because of the apparent safety and specificity of naltrexone therapeutic action, it can be a viable option in a person with autism with clinically significant self-injurious behavior.[80,82]

The current dearth of evidence-based psychopharmacologic and behavioral research in persons with autism is being addressed by a developing network of National Institute of Health (NIH) funded research centers, such as Research Units of Pediatric Psychopharmacology (RUPP), Centers for Programs of Excellence in Autism (CPEA), and Studies to Advance Autism Research and Treatment (STAART). The mission of these units is to foster well-controlled, multicenter, behavioral and psychopharmacologic intervention studies targeting behavioral symptoms in persons with autism.[48]

Among a number of scientifically unsupported treatments for autism is secretin, a polypeptide hormone promoted in the late 1990s as an efficacious therapy. Controlled trials found no reliable evidence of such efficacy.[83] Other popular therapies that have been subsequently found to have no scientific basis of efficacy include elimination diets in which casein (from wheat products) or gluten (from dairy products) are removed from the diet, facilitated communication (based on the idea that autism is a disorder of expression as opposed to language, and computer keyboards were used to assist in expressing ideas), megadoses of vitamin $B_6$ in combination with magnesium administration, dimethylglycine (an antioxidant) administration, nonspecific chelation therapy, and famotidine treatment.[84,85]

### CLINICAL CONTROVERSY

In the absence of a wealth of proven drug therapies for the core symptoms of autism, scientifically unsupported treatments are widely promoted and sometimes used. Autism is a chronic, treatment-resistant disorder, and families often seek cures that promise rapid and lasting results.[84] Despite a desire to assist sometimes desperate families, the clinician should examine the evidence-based support of such purported miracle cures prior to recommending or prescribing such treatments.[84]

## EVALUATION OF THERAPEUTIC OUTCOMES

The core symptoms of autism include deficits in social interaction; restricted, repetitive, and stereotypic patterns of behavior, interests, and activities; and deficits in communication and language. Clinical investigators have used a variety of psychometric assessment instruments in attempts to measure changes in core symptoms secondary to treatment interventions.[86] 3 Monitoring the safety, efficacy, and tolerability of psychopharmacologic interventions in persons with autism is imperative to minimize adverse medication-related sequelae, and optimize desired therapeutic outcomes.

There are a variety of instruments reported in the literature that have been developed and used in clinical trials to measure symptoms, such as communication impairment, restricted interests, and repetitive behavior. A review of many of these instruments is available elsewhere.[87] Pharmacotherapy in autism is usually directed toward minimizing maladaptive behaviors, such as irritability; hyperactivity; compulsive, ritualistic, and perseverative behavior; and variants of self-injurious behavior. The Aberrant Behavior Checklist was designed for assessment of behavioral changes in institutionalized individuals in pharmacotherapy trials, however, a community-based version is also available.[88,89] The Aberrant Behavior Checklist consists of 54 items divided into 5 domains: irritability, hyperactivity, stereotypic behavior, lethargy, and inappropriate speech. The lower the score in each domain, the greater the behavioral improvement.

Aggressive medication-related side effects monitoring and assessment is important in this population, as self-reporting can be unreliable and can underrepresent the presence of side effects. An instrument that is caregiver-rated such as the Monitoring of Side Effects Scale can be effective for this purpose. The Monitoring of Side Effects Scale is a multisystem quantitative and qualitative caregiver assessment that rates the presence or absence and severity of a variety of potential medication-related adverse effects for clinician review.[90]

Signs and symptoms are written in layperson language and are listed by body area or system. As such, it is a broad-based screening tool that can be enhanced by side-effects specific scales such as those for akathisia (Barnes Akathisia Scale [BAS]), extrapyramidal effects (Simpson-Angus scale), or tardive dyskinesia (Dyskinesia Identification System: Condensed User Scale [DISCUS]).[91–93]

## RETT'S SYNDROME

8 In 1965 an Austrian physician, Andreas Rett, wrote the first paper documenting a series of developmental changes affecting young girls who appeared to achieve normal developmental milestones then experienced age-related regression. The significance of these findings and the widespread occurrence was not fully apparent until 1981 when similar cases were presented at a conference on developmental disabilities.[94] This syndrome, now known as Rett's syndrome, can represent the most common cause of mental retardation in females in which the degree of mental retardation is greater than mild.[95] Seizures and scoliosis are frequent comorbidities, both of which can significantly impact the quality of life. The primary goals of treatment are to optimize seizure control and mobility.

## EPIDEMIOLOGY

The prevalence of Rett's syndrome can depend on the population surveyed. Higher population bases are associated with lower prevalence rates. One estimate, based on smaller sample sizes, places the occurrence as 1 in 10,000 to 15,000.[95]

## ETIOLOGY AND PATHOPHYSIOLOGY

Rett's syndrome is associated with an X-linked mutation, specifically at the X28q site.[95] The specific mutation involves the methyl-CpG-binding protein 2 (MeCP2).[95–97] This is the most common mutation for Rett's syndrome and has been identified in approximately 80% of those diagnosed with classic Rett's syndrome.[96,97] There is evidence to support that mutations at this gene site can alter the behavioral phenotype (body rocking, stereotypic hand movements), severity, and survival rates of Rett's syndrome.[96–98] These genetic mutations, however, might not fully account for the development of Rett's syndrome.

In addition to genetic mutations, structural changes in the brain have been identified as another possible etiology for Rett's syndrome. It has been theorized that the foundation for the different regressive stages in Rett's syndrome is a change in specific areas of the brain as it matures. Developmental motor delays (including weak muscle tone and coordination difficulties)[99] are a function of lesions in the brainstem and midbrain. A lesion in the raphe nucleus and/or the locus coeruleus has been proposed. If functionality in these areas is impaired, the dopaminergic neurons are less active. Over time, hypoactivity leads to an upregulation of dopaminergic receptors resulting in the stereotypic hand movements identified as one of the core features of classic Rett's syndrome.[99] Over time, severe to profound mental retardation manifests, and the progressive loss of motor skills becomes more prominent than the autistic features. Other neurologic structural changes, such as fewer neurons in the substantia nigra[95] have also been noted, but findings are inconsistent.

### CLINICAL PRESENTATION OF RETT'S SYNDROME[1,94,95]

**General**

- Rett's syndrome is diagnosed primarily in females.
- Previously acquired skills are lost following an apparently normal prenatal and early development.
- Rett's syndrome can represent the most common cause for mental retardation in females, when the level of disability exceeds mild.
- Diagnostic criteria have been identified for a classical form and variant form of Rett's syndrome.

**Diagnostic Features for Classic Rett's Syndrome**

- Following a relatively normal period of growth and development, there is a slowing of development at approximately 4 to 6 months of age.
- One of the first indicators is slowing of head growth.
- Social interactions are lost, and stereotypies can be seen.
- Previously acquired skills are lost, and progressive neurologic impairment is seen, particularly hand skills and the ability to ambulate.
- Rett's syndrome is generally associated with severe to profound mental retardation.

**Diagnostic Features for Variant Rett's Syndrome**

- The female is at least 10 years old before the diagnosis is made.
- Skills can be partially lost rather than the total loss experienced with the classic form.
- No other cause of the mental retardation can be identified.

**Other Diagnostic Considerations**

- There is an increased risk for seizure disorders in the Rett's syndrome population compared to the general population.
- Neurologically-mediated scoliosis can appear and can be severe.

## CLINICAL PRESENTATION

Rett's syndrome is a genetically based disorder characterized by a developmental regression. Some genetic variations have been identified that are thought to moderate the symptoms and progression of Rett's syndrome, the extent to which is not fully known. Classical Rett's syndrome is now considered to account for approximately 80% of the Rett's syndrome cases diagnosed.[94,100] Atypical or variant Rett's syndrome, the features of which are outlined in Table 76–4, accounts for the remaining cases.[94] It is considered a neurodevelopmental disorder rather than a progressive neurodegenerative disorder.[94]

8 Current diagnostic criteria include an uneventful pregnancy and birth followed by seemingly normal development for the first 4 to 6 months during which normal developmental milestones are achieved. Head circumference is within normal limits at birth. The timeframe can vary slightly but generally between 6 months and 4 years of age, head growth ceases. This can be considered an indicator that brain growth is

**TABLE 76-4 Supportive Features of Rett's Syndrome**

The following features are not included in current diagnostic criteria but are used to help identify variant Rett's syndrome:

- Breathing irregularities, including bloating and air swallowing
- Bruxism
- Gait dyspraxia
- Neurologically-mediated scoliosis
- Neurologically-mediated lower limb changes
- Autonomic peripheral circulatory impairment
- Presence of EEG changes characteristic of Rett's syndrome
- Unprovoked laughing and/or screaming
- Intense eye communication

The presence of 5–6 of these supportive findings supports a diagnosis of variant Rett's syndrome.

EEG, electroencephalogram.
*Data from Hagberg[94] and Hagberg et al.[100]*

**TABLE 76-5** Rett's Syndrome Stage

| Stage | Onset Age | Duration | Characteristics |
|---|---|---|---|
| I | 6–18 months | Months | Developmental slowing<br>Head growth ceases<br>Social withdrawal<br>Loss of purposeful hand movements |
| II | 1–4 years | Weeks to months | Onset of severe to profound mental retardation<br>Breathing irregularities<br>Autistic features<br>Seizures can appear |
| III | 4–8 years | Years | Seizures increase<br>Partial return of language skills<br>Deterioration slows<br>Can be ambulatory |
| IV | >8 years old | Decades | Scoliosis<br>Dystonias<br>Can have lower limb wasting |

*Data from Hagberg[94] and Glaze.[101]*

also affected. During this time, previously acquired developmental milestones are lost, including motor skills, communication, and interactions with parents and the environment. One of the key diagnostic features that appears between ages 1 and 4 years involves loss of purposeful hand movements, replaced with stereotypies (hand-wringing or clapping and hand-washing movements). Lower limb control is also lost during this period. Once the key features are present, generally between 2 and 5 years of age, a diagnosis of Rett's syndrome is made.[100]

8 The order of symptom appearance and somewhat age-dependent regressive changes associated with Rett's syndrome distinguish it from other developmental disorders. The developmental changes can be grouped into four stages (Table 76–5). Stage I is characterized by developmental stagnation, at approximately 6 months of age, after initially meeting developmental milestones. Additional features are skill regression and head growth deceleration. Further changes might not be seen for 1 month to 18 months. Stage II is characterized by a more rapid regression and is known as the rapid destructive or developmental regression stage.[94,95] Key features in this stage are the emergence of stereotypic hand movements, dementia, coordination changes, and irregular breathing. Language skills can also be lost, and seizure activity can start.[94,95] The duration of this stage can range from weeks to 1 year. The onset of stage III is highly variable (between 3 or 4 years of age up to 8 years of age). This stage is referred to as pseudostationary. Previously lost skills, like language, can partially reappear. Motor skills might or might not be developed enough for walking. Complex partial or generalized tonic-clonic seizures appear, if not already present in stage II. There is no additional regression, although the deficiencies that appeared in stage II remain. The time course for this stage, which varies widely, can last into young adulthood or beyond. Stage IV is characterized by late motor deterioration. Lower limb dystonia and wasting can occur and feet can be cyanotic. At this stage ambulatory ability is lost. Scoliosis, often severe and neurologically-based, is common. This stage can last for decades.[94,95,101]

The diagnostic criteria are helpful in the identification of the majority of the cases. Not all cases, however, fit the classical representation. A differing presentation was described by Hagberg and colleagues.[100] Consequently, criteria to identify variant Rett's syndrome were introduced.

In variant Rett's syndrome, females still account for the majority of the cases, but the onset is not within the first 6 months as for the classic form. In the variant form, the female is at least 10 years old at onset. 8 Some of the features of the classic form, such as loss of fine finger skills, early changes in communication, and head growth cessation or deceleration are also needed to meet diagnostic criteria for the variant form. However, these changes may not be as marked and can represent a partial skill loss. Head circumference can still be within normal limits, or it can measure two standard deviations below the mean. The cause of mental retardation is unexplained by other factors.[94,100]

Additional features for variant Rett's syndrome are also seen in classic Rett's syndrome but are not needed to meet diagnostic criteria. These features include abnormal breathing, bloating from air swallowing, bruxism, scoliosis, autonomic nervous system impairments, and behaviors, such as sudden laughing or screaming. Communicating by intense gaze or eye pointing is common.[100]

The development of stereotypic hand movements, social and environmental withdrawal, and abnormal sleep patterns have given rise to investigating if Rett's syndrome is a variant of autistic disorder.[102] Although impairments in communication and interaction with the environment are distinguishing features in autism, one differentiation between Rett's syndrome and autism is the intense eye gaze and eye pointing communication style seen in women with Rett's syndrome. This endures into adulthood.[94] In addition, stereotypical hand movements and breathing abnormalities, components of the diagnostic criteria for Rett's syndrome, are not prominent features in autism.[102] Features supportive of the variant Rett's syndrome diagnosis are found in Table 76–4.

# TREATMENT

## Rett's Syndrome

Both nonpharmacologic therapies and pharmacotherapy interventions have been used for medical comorbidities of Rett's syndrome.

### NONPHARMACOLOGIC THERAPY

After the diagnosis of Rett's syndrome is established, the clinician should generally provide or recommend family counseling to families and caregivers to help them adjust to the needs of their special child.

8 Scoliosis, the most common orthopedic problem in Rett's syndrome, is a function of neurologic development and is age-related. It is unaffected by improved nutrition or nutritional status. Lessening the severity of scoliosis is important in maintaining mobility, decreasing breathing problems, and improving bowel function.[103] Less invasive techniques than surgical intervention have been tried (e.g., aggressive physical therapy and splinting), but effectiveness was inconsistent and can be a function of curvature severity.[103,104] Early, consistent intervention is recommended if using prostheses.[104]

Behavioral interventions for hand stereotypies, the most prominent feature of Rett's syndrome, have been tried. Positive results were reported, although generalizability is limited by small sample sizes. Functional analysis of the behavior did not support that stereotypies were maintained by environmental reinforcers. Repetitive hand movements appear to be mediated by autonomic mechanisms or maintained by neurochemical/neurobiologic mechanisms.[105,106]

### PHARMACOLOGIC THERAPY

There is little information on the pharmacologic treatment of patients with Rett's syndrome in the peer-reviewed literature. Comorbid medical conditions impact and can limit drug selection. Comorbidities include cardiac problems and seizures. A prolonged corrected QT interval (QTc) is one of the primary cardiac problems in Rett's syndrome.[107] Enhanced sympathetic nervous system activity and a prolonged QTc have been linked to an increase in sudden deaths and serious cardiac arrhythmias in individuals with Rett's syndrome compared to the general population.[101,108] The pathophysiologic basis is not known; however, it can be linked to a dysfunction in the

serotonin system.[109] Concurrent administration of medications that prolong the QTc (e.g., imipramine, chlorpromazine) should be done with caution and electrocardiographic monitoring.[110]

Physiologic changes in cardiac function are a function of age and clinical stage in patients with Rett's syndrome.[109] A small observational study ($n = 28$) designed to assess for a relationship between cardiac dysautonomia and serotonin serum levels was conducted in untreated participants and those receiving either valproate or carbamazepine for seizures. The treated group ($n = 18$) had higher plasma serotonin concentrations than the untreated group ($n = 10$). This can be a medication-mediated effect, however. It was suggested that use of an SSRI might improve sympathovagal imbalance, however, no specific pharmacotherapeutic recommendations were made.[109] Drug therapy selection must be made in consideration of cardiac implications and potential drug side effects.

Pharmacotherapy is not effective as an intervention for the loss of previously acquired skills, hand-mouthing, stereotypies, problems with sleep, anxiety, or low mood. In a case report, olanzapine was effective in reducing long, unprovoked screaming episodes, severe agitation, hair pulling, and self-injury unresponsive to prior trials of typical and atypical antipsychotics, anticonvulsants, and benzodiazepines.[111]

An active seizure disorder was found in more than 90% of a representative sample ($n = 53$) of females with Rett's syndrome.[112] Complex partial or generalized tonic-clonic seizures were the most common types. Little published information on the treatment of Rett's syndrome-associated seizures is available. Seizure frequency decreases after 20 years of age, and more partial seizures are reported, whereas generalized tonic-clonic seizures are more common at initial diagnosis.[112] Seizure activity was evaluated in 50 females in this group. Active epilepsy (defined by at least two epileptic seizures without an identifiable cause, excluding neonatal seizures) was considered to be present if a seizure occurred within the last 5 years. Head circumference was found to be associated with seizure activity onset, and greater seizure frequency was associated with decreased head circumference. EEG evaluation found that commonly reported vacant staring spells were not always epileptic in origin. Staring, hyperventilation, episodic laughing, and episodic crying were also frequently reported events, possibly not epileptic in origin, which were not evaluated by neurologists.[112] Randomized, placebo-controlled trials have not been conducted to explore management of seizures in patients with Rett's syndrome.

Lamotrigine was used in two cases of Rett's syndrome in females with language regression and seizures. Following initiation of therapy with lamotrigine, seizures were controlled, and both hand stereotypies and other autistic behaviors decreased. In each case, lamotrigine was dosed 3 mg/kg per day. Lamotrigine was adjunctive therapy to valproic acid in one case.[113]

### CLINICAL CONTROVERSY

Rett's syndrome is associated with the development of seizures, often refractory to anticonvulsant treatment. Although controversial, the ketogenic diet, a high-fat, low-carbohydrate diet with adequate protein, can provide an alternative treatment modality for seizures in such cases. A prospective study ($n = 65$; non-RS children) evaluating the impact of this diet on behavior, development, and parental stress reported significantly reduced daily seizure frequency and improved behavior (attention and social functioning) at 1-year followup.[114]

## EVALUATION OF THERAPEUTIC OUTCOMES

The most medication-responsive feature of Rett's syndrome is seizure activity. Seizure frequency and presentation change with age.[112] If drug therapy results in a reduction in seizure frequency, therapy is considered effective. Depending on the anticonvulsant used, laboratory monitoring can be needed (see Chap. 58). Adverse effects should be scrupulously monitored when medications are added or doses are changed and at regular intervals thereafter. During the late teens and twenties, reassessing the need for continued treatment is recommended.

## CONCLUSIONS

Developmental disabilities or mental retardation are commonly identified in childhood or adolescence. There might or might not be a genetic component, and often the cause can be unknown. Persons with DD are at significant risk for psychiatric comorbidities. In the absence of randomized controlled trials, most treatment modalities attempt to minimize documented, critical medication-responsive target behaviors. Effective treatments require interdisciplinary care and ongoing monitoring for response and potential medication-related side effects.

## ABBREVIATIONS

AAP: American Academy of Pediatrics
ABS: Adaptive Behavior Scale
AD: Alzheimer's disease
ADD: attention deficit disorder
AL: acute leukemia
AML: acute myelogenous leukemia
BAS: Barnes Akathisia Scale
CARS: Childhood Autism Rating Scale
CBT: cognitive behavior therapy
CPEA: Centers for Programs of Excellence in Autism
DD: developmental disability
DISCUS: Dyskinesia Identification System Condensed User Scale
DS: Down's syndrome
ECT: electroconvulsive therapy
EEG: electroencephalogram
FDA: Food and Drug Administration
GABA: $\gamma$-aminobutyric acid
MeCP2: methyl CpG binding protein 2
NIH: National Institute of Health
NMDA: N-methyl-D-aspartate
NPI: Neuropsychiatric Inventory
PDD: pervasive developmental disorder
QTc: corrected QT interval (adjusted for heart rate)
RUPP: Research Units of Pediatric Psychopharmacology
SIB: Severe Impairment Battery
SSRI: selective serotonin reuptake inhibitor
STAART: Studies to Advance Autism Research and Treatment

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