Chapter e93: Developmental Disabilities

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KEY CONCEPTS

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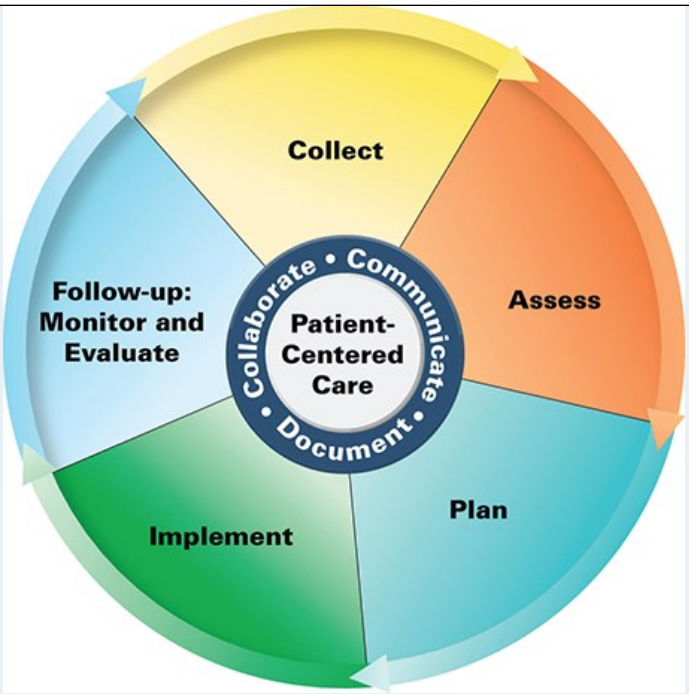
1. People with intellectual and developmental disabilities (IDD) have higher incidence of mental illness and challenging behaviors, with dual diagnoses being common.
2. Persons diagnosed with Down syndrome (DS) can be at increased risk for medical and psychiatric comorbidities.
3. People with IDD experience high rates of polypharmacy and polypsychotropic medication use. Assessment should include physical disorders, as well as social and environmental factors complicating their care.
4. People with DS have higher rates of Alzheimer-type dementia. A thorough evaluation is needed to differentiate between depression and Alzheimer disease (AD).
5. Treatment plans for persons with autism spectrum disorder (ASD) focus on increasing social interactions, improving verbal and nonverbal communication, and minimizing the occurrence or impact of ritualistic, repetitive behaviors and other related mood and behavioral challenges (eg, over activity, irritability, and self-injury).
6. Many purported pharmacologic and nonpharmacologic treatments for ASD lack objective evidence-based support.
7. A structured teaching approach focusing on increasing social communication and integration with peers is needed when providing services to persons with ASD.
8. Nonpharmacologic interventions for sleep disturbances in individuals diagnosed with ASD should be implemented prior to pharmacotherapy considerations.
9. Psychopharmacologic treatment planning should include monitoring of objective, measurable medication-responsive target behaviors and assessment of potential adverse effects, which are of critical importance when treating the behavioral challenges of ASD. Furthermore, the response of individuals to pharmacotherapy is highly variable.
10. The use of FDA-approved medication for off-label indications is an acceptable clinical practice if founded on evidence-based research and includes informed consent.

PATIENT CARE PROCESS

Patient Care Process for Intellectual and Developmental Disabilities



Collect

- Involve the patient and one or more caregivers in this process
- Patient characteristics such as age, sex, pregnancy status
- Past medical and psychological history
- Previous life events (eg, changes in living situation)
- Social history (tobacco/ethanol, substance use or misuse) and dietary habits
- Social and community-based activities
- Current prescription and nonprescription medications and supplements

Assess

- Contraindications to potential medications
- Psychotropic medication already prescribed
- Presence of adverse effects from medications
- Physical causes for challenging behaviors such as constipation, gastroesophageal reflux, seizure, aspiration, pain including dental-related pain, sleeping problems (Table e93-1)
- Risk or evidence of harm to self, others, or property
- Frequency of challenging behavior
- Patient's preference for a type of therapy if appropriate and identify those involved in the patient's medication use process

Plan*

- Choose medication with the strongest evidence and minimal adverse effects (Table e93-2)
- Determine potential medication interactions with other medications
- Use supported decision making, which includes patient preferences, when able
- Education for patient and caregivers
- Develop non-medication intervention based on social and personal factors
- Type of prescription medication insurance and insurance-related regulations in choice of medication

Implement*

- Provide patient education to patient and caregiver(s)
- Work to understand issues related to medication adherence. Choose dosage form that will reduce the likelihood of nonadherence

Follow-up: Monitor and Evaluate*

- Reduction in frequency and severity of challenging behaviors
- Presence of adverse effects (Table e93-2)
- Patient adherence to therapy
- Patient's ability to engage in activities in the community
- Caregiver(s) understanding of therapy
- Medication interactions with other medications

****Collaborate with patients, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Compare and contrast the Patient Care Process and the assessment and follow-up tools available on the website for "Healthcare for Adults with Intellectual and Developmental Disabilities. Toolkit for Primary Care Providers." https://iddtoolkit.vkcsites.org/

Behavioral Problems and Emotional Concerns-Primary Care Provider Checklist

Psychiatric Symptoms and Behavior Checklist

Psychotropic Medication Checklist

Management Plan

Compare and contrast the criteria for each step of the PCP with those of the Toolkit Behavioral and Mental Health Issues "Behavioral Problems and Emotional Concerns-Provider Checklist," the "Risk Assessment Tools for Adults with IDD in Behavioral Crisis," and the "Psychotropic Medication Checklist." This activity will help you envision the important points to assess when consulting on a patient who has an IDD and challenging behavior.

INTRODUCTION

Developmental disabilities (DD) are chronic disabilities that can be cognitive, physical, or both. They appear before the age of 22 and are likely to be lifelong.[1] Some DDs are largely physical challenges, such as cerebral palsy or seizure disorders, and some individuals may have a condition that includes both a physical and an intellectual disability. Intellectual disability (ID) is a disability characterized by significant limitations in both intellectual functioning and adaptive behavior, which covers many everyday social and practical skills.[2] This chapter will use the term "intellectual or developmental disabilities" (IDD) to refer to people who have conditions associated with DD, ID, or both.

EPIDEMIOLOGY

Down syndrome and autism spectrum disorder are several of the more common diagnoses which make up IDD. About 1.5% to 2.5% of the US population is living with some form of IDD.[3] The actual frequency and per cent of the US population characterized as having IDD varies based on the data source and the definition used. According to the 2010 US Census Bureau, 1.2 million adults (0.5%) had an ID and 944,000 (0.4%) had a DD.[4] Globally, the prevalence of ID is about 1% of the population.[5] People with IDD primarily live in the community in living situations that include living with family (71%), group homes, or in supported living arrangements (eg, living by themselves or with one or two roommates with an aid). Only 13% of adults with IDD live in supervised residential settings.[6]

1 People with IDD often have some degree of cognitive impairment that may limit their ability to be a collaborative partner in the medication use process, increasing their risk for medication-related problems. Furthermore, those with IDD generally have a high burden of illness which often leads to the person taking multiple medications.[7] Compared to the general population, these complex medication regimens increase the individual's risk for adverse events.[8] Caregivers provide a wide range of support to the person with IDD, depending on the functional ability of the person, including assisting them in navigating the medication use process.[3] In a 2013 population health survey of people who have IDD, 88.3% of people between the ages of 18 and 39 years and 94.7% of those over age 60 years were taking a chronic medication.[9] The prevalence of polypharmacy, with five or more medications, ranged from 30.4% to 45.5% of people who have IDD, with higher rates being seen in older people.

Mental Illness/Dual Diagnosis

Although age-related chronic illness develops in people with IDD similarly to the general population, some conditions may be more prevalent, or occur at an earlier age. The focus of this chapter is on the mental health and behavioral issues that occur in people with IDD. For the purpose of this chapter, the term "dual diagnosis" refers to a person with IDD and who also has a comorbid mental illness. The prevalence of mental disorders in people with IDD is higher than in the general population. Also, challenging behaviors such as aggression or self-injurious behaviors are seen in some people with IDD and are strongly associated with psychotropic medication prescribing, often with multiple psychotropic medications.[10] Psychiatric disorders in persons with an ID, such as depression and anxiety, may result from environmental variables (eg, transitions from family home to group home, change in caregivers), personal variables (eg, age, level of disability, comorbid medical conditions), and the extent to which the individual can cope. The association of life events with depression and anxiety was researched in a community-based population of patients with IDD receiving services from three organizations. Almost all of the subjects (99.1%) had been exposed to at least one life event during the prior 12-month period, with older subjects experiencing more events.[11] In general, more episodes of major depression, generalized anxiety disorder, and panic disorder were associated with a greater number of negative life events. Therefore, clinicians must be aware of the influence of negative life events on a person with IDD when assessing reasons for challenging behaviors.

The prevalence estimates of mental illness or challenging behaviors in people with IDD range from 30% to 70%.[12] The range of findings can be attributed to a variety of factors including differences in population sampling and methodologies used in identifying psychiatric disorders in persons with IDD. Psychiatric disorders may manifest differently among individuals with IDD compared to the general population. Estimates of the prevalence of mental illness for patients with IDD may not be entirely accurate, due to difficulties applying diagnostic criteria, difficulty accessing services, and clinical presentation that may be difficult to interpret.[13] One study of 1,023 people with IDD, which employed a comprehensive individualized clinical assessment, revealed a rate of mental illness of 40.9%.[14] The National Core Indicators project identified a rate for mental illness or psychiatric diagnosis of 66% (N = 19,657) for adults who have IDD.[15] The prevalence of challenging behaviors in people with IDD is also high, with percentage of populations varying from over 5% to 17%.[16]

Challenging/Self-Injurious Behaviors

Challenging behaviors may be seen in patients with IDD and include aggression, self-injury, and property destruction that is often lifelong and can result in negative outcomes such as physical injury and social isolation.[17-19] Importantly, challenging behaviors serve different functions and many factors contribute to their occurrence.[20] Mental health disorders and challenging behavior in people with IDD may be associated with sensory impairments, negative life events, lack of suitable supports (eg, emotional, social, community, work, and recreational), stress, and limited coping capacity.[21-23] Challenging behaviors may also be associated with early victimization, non-enriched and restrictive environments during both childhood and adulthood, traumatic brain injury, skill deficiencies in anger management, poor social skills, communication deficits, and psychopathology. Symptoms related to medical causes or medication-related adverse events may be expressed behaviorally and misinterpreted and reported as challenging behavior.[24]

About 10% to 15% of people with IDD engage in some form of challenging behavior,[25] such as self-injurious behavior (SIB) which is defined as behavior in which a person harms or attempts to harm themselves deliberately and physically. Examples include head banging, self-biting, and self-scratching. The prevalence rate of SIB varies from 4% to 23% of people with ID.[26] According to the results of a study using the National Core Indicators database (2015-2016), 23.2% of adults surveyed who have IDD needed some or extensive support for SIB.[27] Individuals who required at least some support for SIB were found to have fewer relationships, less inclusion in their communities, and poorer employment outcomes. Notably, SIB, when present, may occur persistently over time and may be associated with a number of causes such as genetic, biological, psychological, environmental, or a combination.[28] It is also found more commonly in conditions such as Fragile X syndrome, Prader–Willi syndrome, Cri du Chat syndrome, and Lesch Nyhan syndrome.[26] Challenging behavior should not be considered a problem associated with an individual, but should be regarded as the result of an interaction between the individual and their environment. The use of positive behavioral supports is gaining acceptance as an alternative form of treatment for SIB.[29] When working with patients who have IDD and mental illness and/or challenging behaviors, clinicians can screen for sensory impairments, negative social circumstances, stressful life events, and coping capacity. Family and caregivers may be counseled on the value of promoting friendships, social networks, and accommodations for inclusion and participation to decrease isolation and loneliness.[30,31] Antipsychotic medications are often prescribed to control challenging behaviors, often before nonpharmacologic intervention or with no long-term planned tapering.[32] The combination of poor communication skills, co-occurring mental illness, and severity of ID all contribute to the use of psychotropic medication to control challenging behaviors.[24]

Diagnostic overshadowing is a potential cause of mis- or under-diagnosis of mental illness in people with ID.[33,34] This refers to clinicians overlooking or minimizing the signs of psychiatric disturbances in a person with an ID, and attributing signs and symptoms of mental illness to the cause of IDD. Another problem of diagnostic overshadowing is misinterpreting the symptoms of a somatic medical condition to that of challenging behavior or mental illness. According to a multiyear observational registry study comparing psychiatric diagnoses and somatic comorbidities of older adults with IDD compared with the general population, the low occurrence rate of somatic diagnoses may be the result of those conditions being overshadowed by the high degree of psychiatric comorbidities.[35]

DOWN SYNDROME

Down syndrome (DS) is associated with common dysmorphic features and a wide range of medical and psychiatric concerns, including a number of developmental abnormalities. Congenital heart defects, seizure disorders, orthopedic abnormalities, sensory defects, leukemia, disorders of the eye (eg, cataracts, glaucoma), gastrointestinal (GI) tract, immune system, skin, and thyroid gland are all associated with DS. Persons diagnosed with DS also have a high probability (30%) of early-onset Alzheimer disease (AD) (see later section).[36] DS is one of the most common conditions associated with IDD.[37] The live birth prevalence is approximately 1 in 700 live births.[38]

ETIOLOGY

Chromosomal analysis has identified the etiology of DS as the presence of an extra chromosome 21, which has led to the alternative name of trisomy 21, as this represents one of the most studied abnormal chromosomal conditions. Chromosomes naturally divide and separate in a process known as disjunction during meiotic division. However, in DS, the chromosomes fail to fully separate and both chromosomes remain in the same cell. The end

result is an abnormal number of chromosomes on each strand. For many years, advanced maternal age has been recognized to positively correlate with an increased risk for DS, particularly over age 35 years.[39] Consideration has also been given to paternal age as data shows that for couples with younger fathers, the odds of having a child with DS were increased almost twofold.[40] Additionally, it has been theorized that two variables, lack of maternal folic acid supplementation and genetic variability that decrease enzymatic processes in folate pathways, may negatively impact meiotic nondisjunction of chromosome 21. However, the National Down Syndrome Project found no association between folate supplementation use and nondisjunction based on younger maternal age (less than 35 year) or ethnicity, but did report an association between older maternal age and a later stage of oocyte meiosis (meiosis II nondisjunction). While these results may explain previously reported finding differences, additional confirmation, controlling for maternal age, is needed.[41]

CLINICAL PRESENTATION

The consequences of this chromosomal variance include characteristic facial features, some degree of ID, hypotonia, an increased risk for congenital heart disease, and early-onset AD.[42,43] The characteristic facial features make children with DS more readily identifiable at birth with ID ranging from mild to severe.[42] In addition, individuals with DS appear to be at risk to develop depression, anxiety, and obsessive–compulsive disorder.[44] The differential diagnosis for mood disorders in all patients with DS should include an evaluation of thyroid function, as the clinical signs and symptoms of hypothyroidism and dementia can mimic some features of depression. The risk of a thyroid disorder as a comorbidity in people with DS is estimated at 4% to 18%.[42] In a study of older Medicare beneficiaries with DS in California, 40% were identified as having dementia. Comorbid conditions were more numerous among those with dementia compared to those with DS without dementia, especially among those younger than 65 years. These conditions included hypothyroidism, anemia, seizure disorder, and weight loss.[45]

CLINICAL PRESENTATION: Down Syndrome

Diagnostic features

- Facial features can suggest DS, but an additional diagnostic evaluation is necessary.
- Degree of ID ranges from mild to severe.
- Growth delays are common.

Common physical characteristics

- Hypotonia can be evident at birth.
- Facial features include flat nasal bridge and profile, with up-slanted eye folds.
- The palate can be narrow and the neck thick and broad.
- Hands are characteristically short and broad.

Other clinical concerns

- Comorbidity with mental illness, challenging behaviors, and self-injurious behavior.
- An increased risk for congenital heart problems; a cardiac evaluation is generally done shortly after birth with periodic follow-up.
- Congenital cataracts, hearing and sight problems, and hypothyroidism are common.
- Leukemia may occur in early childhood.
- Features of AD can present by the third or fourth decade.

TREATMENT

Desired Outcomes

Treatment goals in DS are to identify medical and psychiatric comorbidities, set realistic goals, and provide effective social, environmental, nonpharmacologic, and pharmacologic interventions to improve the quality and length of life.

General Approach to Treatment

Medical screenings in patients with DS should assess for hypothyroidism, cardiac problems, sensory impairments (including hearing loss secondary to chronic otitis media with effusion or vision defects due to congenital cataracts or glaucoma), and GI problems (including constipation and celiac disease).[42] Guidelines for health supervision and anticipatory guidance in infants, children, and adolescents with DS are available through the American Academy of Pediatrics (AAP).[43] Guidelines for the medical care of adults with DS are also available and routine screenings are also recommended throughout the course of life to address psychosocial changes, potential residential or vocational stressors, and the consequences of aging.[38]

Nonpharmacologic Therapy

The use of social supports for both individuals with DS and their family may help in the development of functional adaptive skills and therefore the fulfillment of the potential for the person with DS. Family education and support network development can assist caregivers by providing tools and resources necessary to more effectively manage persons with DS, allowing these persons to achieve their full potential.

Depressive Symptoms and Challenging Behaviors

All mental health treatment modalities available to the general population also apply to those with DS, with nonpharmacologic options for depression including psychotherapy and electroconvulsive therapy (ECT).[42] Information on the effectiveness of ECT in the DS population is limited to case reports. If communication skills are adequate, psychotherapy may also be an option with treatment strategies including psychodynamic and cognitive behavior therapy (CBT). While the applicability of psychotherapy can vary with the level of ID, for persons with mild intellectual impairment and depression, this treatment modality may be beneficial. These current behavioral therapy models are more effective in addressing specific problematic behaviors rather than the underlying emotional problems of persons with ID. Furthermore, the extent to which these strategies translate to persons with DS and more severe ID is not known.[42,46]

Pharmacologic Therapy

Depressive Symptoms

Pharmacotherapy for the treatment of depression in patients with DS follows guidelines used in the general population. For more information on the treatment of depression, see Chapter 88, “Depressive Disorders.” Features of depression commonly seen in persons with DS, in order of frequency, include apathy, disordered sleep, and changes in weight. Difficulty identifying depression in this population is impacted by the level of cognitive impairment, the ability to express abstract concepts (eg, helplessness or hopelessness), and the level of adaptive functioning.[42] Clinical trials focused specifically on this population are few, and most information has been based on small studies or case reports. Efficacy with SSRIs and amitriptyline is reported in the DS population. If psychotic features (eg, delusions, hallucinations) are present, low-dose antipsychotic augmentation is recommended. In the studies reviewed, treatment duration was 2 to 3 years.[42]

As with the treatment of depression in the general population, the medication trial is of appropriate dose and duration before deeming the patient to be a non-responder. Furthermore, ruling out comorbid medical conditions that could contribute to depression is essential.

Challenging Behaviors

People with IDD are prescribed psychotropic medications at a rate higher than the general population,[47] which is not only due to an increase in the

diagnosis of psychiatric illness within this population, but also because of challenging behaviors not always associated with psychiatric illness. The most common class of medication dispensed was antipsychotics (21.1% of adults with IDD), according to a study of administrative pharmacy claims data of over 52,000 people with IDD.[48] The use of psychotropic medication in adults living in group homes in the Netherlands was also high with the primary reason for use being behavioral issues. The authors hypothesize that the group home staff found it difficult to deal with people who exhibit socially disruptive behavior.[49] In a cross-sectional study conducted in the Netherlands, out of 2,373 adults with ID, 32.2% received antipsychotic medications. In only 22.5% of cases was the antipsychotic ordered for a psychotic disorder or psychotic symptoms. The remainder of the people received antipsychotic medication for behavioral problems.[50] The presence of adverse events in patients with IDD taking psychotropic medications is a challenge, with adverse events reported in 84% of respondents in a small study in the Netherlands. Not only were symptoms reported, but quality of life was found to be lower in patients with adverse events related to medication.[51] A high incidence of movement-related adverse events is prevalent in adults with IDD taking psychotropic medications.[52,53]

Medication management for challenging behaviors or SIB, using risperidone for example, may be effective in both adults and children, with other second-generation antipsychotics having limited evidence to support their use.[54] In general, antipsychotic medication has been used to treat aggression; however, the rationale for the use of these medications is generally lacking. Aggression is a component of a challenging behavior, and ranges in prevalence from 11% to 27% of people with IDD. Similar to SIB, risperidone is the only medication with some evidence to support its use for aggressive behaviors.[54] There are no reliable data to support antidepressants, other antipsychotic or antiseizure medications for the treatment of aggression.[55,56] Before prescribing medication, clinicians should complete an in-depth assessment of the behaviors and consider nonmedication-based management options as part of the plan.

Sleep Disorders

Obstructive sleep apnea rates are estimated at 50% to 75% in the DS population.[42] Daytime drowsiness and problematic behaviors may be indicative of both an affective disorder, such as depression, and a medical condition secondary to DS. A comprehensive evaluation, including the impact of obesity on sleep, is needed prior to the addition of pharmacotherapy. However, before adding new medication, the medication list for each patient should be carefully reviewed for potential medication interactions and medication–disease contraindications. Parasomnias have been reported with some agents (eg, zolpidem),[57] and the use of medication with this potential effect may require additional monitoring by caregivers, although the frequency of this effect has not been well documented.[58] More information regarding sleep disorders, in general, can be found in Chapter 92, “Sleep Disorders.”

ALZHEIMER DISEASE IN DOWN SYNDROME

4 Persons with DS are at greater risk for AD with increased age, with the proportion of the population affected doubling every 5-year period through 60 years old. Approximately half of people with DS at age 60 have Alzheimer associated dementia, and by age 72 years, the prevalence is 6.

ETIOLOGY

Neuritic plaques and neurofibrillary tangles are the hallmarks of AD. In addition, a gene for amyloid-β precursor protein is located on chromosome 21, which may potentially explain the close relationship between DS and AD regardless of age, gender, and level of ID.[60] While the severity of ID has been theorized to significantly impact the incidence of AD, study results are inconclusive, and the level of ID may limit evaluation. A more extensive discussion of the pathophysiology of AD is beyond the scope of this chapter; more information can be found in Chapter 73.

CLINICAL PRESENTATION

In adults with DS, challenging behaviors, such as aggression, loss of previous skills, and disinhibition, may mark a prodromal presentation of AD. Changes in mood and emotional stability may also present.[61] Assessing changes in functionality and cognition is problematic in this population, particularly in those with greater intellectual impairments. Early studies in this population did not specify the diagnostic criteria used for identification of probable or possible AD. Baseline neurocognitive and behavioral status must be assessed and documented beginning at the age of 40 years, and annually thereafter.[61] To meet the diagnostic criteria, the following are needed: baseline functioning data to assess change, functionality changes not

explained by general aging, and progressive decline.[62] Accurate diagnosis requires use of an appropriate assessment scale for those with DS, such as the Dementia Scale for Down Syndrome and the Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities.[62] In persons older than 40 with DS, behavior changes are the primary features of the early stages of dementia. Changes may be seen prior to onset with higher frequencies of fear, sadness, and overall behavioral regression. Diagnostic criteria for AD include changes in memory, language skills, and activities of daily living. In addition, major functional declines may include behavioral disinhibition, stereotypic or ritualistic behavior, and/or apathy.[62] Risk factors for AD in those with DS include age, genetics, gender, estrogen, multimorbidity, and metabolic syndrome, although information has been limited in some areas. Information on the natural progression of cognitive changes in those with DS and AD continues to emerge. It is important to rule out other causes for changes, such as hypothyroidism, found more commonly in persons with DS compared to the general population. Screening for hypothyroidism should be done every 1 to 2 years, with treatment guided by standard thyroid function studies.[61]

TREATMENT

Desired Outcomes

The therapeutic goal of treatment is to maintain functioning and quality of life close to baseline for as long as possible. Approaches to therapy for persons with DS combined with AD include nonpharmacologic and pharmacologic interventions. As with the general population with AD, treatment of AD for those with DS is multimodal and includes the available treatments and supports in order to maintain functionality for as long as possible. Chapter 73 outlines the treatment of AD in the general population, and this chapter specifically discusses AD in a patient with DS.

Nonpharmacologic Treatments

Traditionally, this population receives some level of residential living supports in either the family home, supported living environment, or a residential facility. Including the caregiver along with the patient with DS in assessment and treatment decisions is important to obtain a complete clinical and home-life assessment.

Pharmacologic Treatments

Pharmacologic treatments neither cure nor stop the pathologic changes associated with AD. The goals of pharmacotherapy in persons with DS and AD, as in the general population of AD patients, are to slow the decline in cognitive function and help preserve activities of daily living to the greatest extent possible. The use of cholinesterase inhibitors and an *N*-methyl-D-aspartate receptor antagonist memantine in the DS population has been studied. Although limited trial data exist related to the use of memantine in the DS population over age 40 years, results from a smaller prospective randomized double-blind trial did not find treatment or control group improvements for cognition and functional abilities. In fact, both groups declined.[63]

The use of rivastigmine transdermal patches for Alzheimer dementia in adults with DS has also been evaluated in a pilot study that included 10 patients; however, significant differences between treatment and historial controls were found. Patch-related adverse effects included erythema, rash, tinnitus, and diarrhea. Problems specific to this population included one participant repeatedly removing the rivastigmine patch which was then followed by marked progression of the disease rendering pharmacotherapy unnecessary.[64] Furthermore, small studies using donepezil piracetam, folinic acid, and memantine, all of which target different pathways and receptors, have also failed to show improved cognition in this population.[65]

While additional information regarding the pharmacotherapy of AD can be found in Chapter 73, preexisting medical comorbidities, such as congenital heart defects, or concomitant pharmacotherapy may limit the use of cholinesterase inhibitors in persons with DS. Clinicians are encouraged to monitor patients receiving cholinesterase inhibitors for commonly reported adverse medication effects and the potential for medication interactions.

A potential neurologic comorbidity of concern in the DS population with AD is seizures. Although seizure activity may increase with age, the distribution of seizure onset is trimodal, with the first peak incidence appearing before 1 year of age (40%) and predominantly consisting of infantile spasms. The second peak occurs between the ages of 20 and 30 years old (40%) and the final peak corresponds to the onset of Alzheimer-related dementia (20%).[61] Advancing age and a diagnosis of DS are independent risk factors for seizures.[66] Therefore, monitoring for new-onset seizure activity and medicating with antiseizure medications, as appropriate, are essential. Seizures can impair cognitive functioning, particularly if not well controlled.[66] More information about seizure disorders, in general, can be found in Chapter 75 “Epilepsy.”

EVALUATION OF THERAPEUTIC OUTCOMES

Baseline functioning must be established early in adult life prior to the onset of AD, which generally begins to occur during the fourth decade of life. This can be particularly crucial in individuals without expressive language skills. Follow-up evaluations should be performed before age 40 years (at least once) then annually.[67] 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 gains have not been observed. Monitoring for potential medication-related adverse effects, including diarrhea, nausea, vomiting, insomnia, and headache, is also essential.

Assessment of therapeutic outcomes for those with DS starts with a thorough multidisciplinary evaluation to establish a baseline problem list, identification of clear therapeutic goals, and valid pharmacotherapeutic rationale to guide medication dosing and adverse medication effect monitoring. An in-depth list of treatment targets, both subjective and objective, is important in persons with DS to assist in evaluation of medication response. Careful monitoring for emergence of potential adverse medication reactions should be regularly conducted and documented as part of ongoing assessment of medication effectiveness and to ensure that adverse medication reactions are not a contributing factor to behavioral changes.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a behaviorally defined pervasive developmental disorder (PDD), which includes autistic disorder, Asperger's disorder, or PDD not otherwise specified.[62] These disorders are grouped together and referred to as autism, or ASD by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). This section focuses specifically on ASD, which is generally characterized by persistent deficits in social communication and social interaction across multiple contexts as well as restricted, repetitive patterns of behavior, interests, or activities. Symptoms must be present in the early developmental period and cause clinically significant impairment in social, occupational, or other important areas of functioning. The disturbances are not explained by intellectual disability or global developmental delay. The severity of ASD is based on the level of support required for social communication impairments and the degree to which restricted, repetitive patterns of behavior impairs functioning.[62,68] Autism is not a disease but a neurodevelopmental disorder with multiple possible etiologies.[69] The onset is typically younger than 3 years of age and is usually, but not always, associated with some degree of ID.[62]

EPIDEMIOLOGY

There has been a recent increase in the reported prevalence of ASD, with the most recent national estimate being 1:68 children identified with ASD.[69] The reported increased prevalence is primarily related to changing and broadening diagnostic criteria, along with an increased index of suspicion, rather than by an actual increased incidence, as ASD is behaviorally identified, and the diagnostic boundaries are not always clear.[70,71] In addition, inclusion of individuals diagnosed with Asperger's disorder and PDD-NOS in newer studies may also be contributing to the increase.[70] Some behaviors (eg, stereotypies) seen in persons with ASD can also be seen in individuals without ASD. There is a significant impact of intellectual ability on the expression of ASD symptoms, which results in a lack of homogeneity in clinical expression of the condition.[72] A recent meta-analysis describes the male:female ratio to be closer to 3:1.[73] When present, ID ranges from mild to severe.

ETIOLOGY

The etiology of ASD is attributed to multiple causal factors, including gene mutations, abnormalities in brain development, and genetic–environment interactions.[72] Autism may occur concomitantly with other developmental disorders that have a known genetic basis such as fragile X syndrome, Rett syndrome, and tuberous sclerosis.[71] Current research primarily focuses on genetics and neuropathology. Although a single genetic mutation or variant leading to ASD is yet to be identified, research findings indicate that structural alterations in the genome DNA, may be involved.[74] Autism may occur concomitantly with a seizure disorder[74] and may be associated with gene defects that are also risk factors for schizophrenia and attention-deficit/hyperactivity disorder (ADHD).

Siblings of affected children have a significantly greater risk of having ASD (3%-18.7%) than those in the general population.[75] According to the results from a national volunteer registry (2,920 children, 1,235 families, a minimum of 1 child meeting ASD diagnostic criteria, and a minimum of 1 full

sibling), the sibling concordance rate was 10.9%, with an additional 8.9% of the siblings demonstrating language delay with autistic-like speech quality.[75]

An additional research further supported the high heritability of ASD outlining that sibling risk varies based on the sex of the index child: 4% versus 7% for female compared with male. If a second child is diagnosed, the risk for concordance in subsequent siblings increases to between 25% and 30%.[76] Lastly, a recent study examined family and twin population-based data across five countries. A high median heritability of 80.8% for autism was found.[77] Heritability refers to how well differences in people's genes account for differences in their traits, with a value of zero indicating almost all variability in a trait is due to environmental factors with little influence from genetic differences. Additionally, children born to older parents appear to be at higher risk for ASD.[71]

While genetics plays a role in the development of ASD, environmental exposures including toxic chemical exposure, teratogens, perinatal insults, prenatal infections, and copper and zinc levels are all under investigation.[71,78] Immunization with measles/mumps/rubella vaccine has been investigated, and no causal association has been identified.[79] Well-conducted case-control cross-sectional ecological and cohort studies investigating the use of thimerosal, an organomercury compound previously used as a vaccine preservative, found no causal association between thimerosal-containing vaccines and the development of ASD or deficits in neuropsychological function.[79] Receiving the MMR vaccine (measles-mumps-rubella) has not been associated with an increased risk of ASD.[80] The neurotoxic effect of mercury exposure continues to be a hotly debated issue among many advocates for persons with ASD, although there is no support for its use. Clinicians must be well informed on this issue to educate parents and caregivers.

PATHOPHYSIOLOGY

ASD may be considered a condition that results from overall brain reorganization beginning early in development.[72,81] There may be alterations in cerebellar structure and connectivity, limbic system abnormalities, and frontal and temporal lobe cortical alterations.[71] ASD may also be conceptualized as a disordering of long-distance cortical and subcortical under-connectivity with compensatory poorly formed shorter circuit over-connectivity. This may lead to enhanced attention on simple stimuli.[78]

Furthermore, dysfunction of virtually all neural systems in the brain has been proposed at some point as a potential basis of ASD.[82] These changes suggest that ASD affects a functionally diverse and widely distributed set of neural systems, making the disorder far broader in scope than a simple social interaction disorder.[82]

There is also research to support the hypothesis that abnormalities in cholinergic receptors and decreases in the nicotinic receptor binding in the cholinergic system, as well as dysfunction in the GABAergic system, may exist in persons with ASD.[83] Other hypotheses of ASD include functional deficits or changes in serotonergic, glutamateric, GABAergic, dopaminergic, cholinergic, and opiate brain systems.[83,84]

Taken all together these studies outline the many differing and often contradictory hypothesis regarding the pathogenesis of ASD.

CLINICAL PRESENTATION

A multiple-step process has been suggested as a structured approach to differential diagnosis of suspected ASD. As a spectrum disorder, the severity or level of impairment within each of these features may be highly variable. Therefore, this structured approach includes a determination of intellectual function and level of language development, followed by assessment of the child's behavior as it relates to chronologic age, mental age, and language age. It is important to identify relevant comorbid medical conditions and the presence of any related contributing psychosocial factors.[71,78,81]

CLINICAL PRESENTATION: Autism Spectrum Disorder

General

- Individuals typically present with delays or abnormalities in social communication/interaction as well as restricted, repetitive patterns of behavior, interests, or activities.

Diagnostic features

- 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.

Data from References 61, 85 and 86.

Between 2% and 21% of those with ASD also have comorbid seizures, which may increase the risk for greater intellectual impairments.[62,85] Other medical comorbidities commonly reported in this population include sleep disturbances, food intolerances, and GI dysfunction.[87] Persons with Down syndrome, Williams syndrome, and fragile X syndrome may have a greater likelihood of having ASD.[88]

The cardinal features of ASD include 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.[62,72] These are primarily manifested as gaze aversion, little/no interest in making friends, preference for solitary activities, repetition of words/phrases, monotone voice, insistence on sameness, and a lack of awareness of other's feelings.[62,72] In most cases (~75%), there is an associated diagnosis of ID, ranging from mild to profound: approximately 30% function in the mild-to-moderate range of ID, whereas 45% to 50% have severe to profound impairment.[89] The risk for development of ASD increases as the IQ decreases.[89] A few individuals with ASD have unusual abilities called splinter functions or islets of precocity. The most significant of these are evidenced in the autistic savant, in which the individuals can have precocity in mathematic calculations, art, music, or rote memory.[62,89]

In many instances, parents note that they were concerned about the child's lack of interest in social interactions since birth, but were sure at least by 3 years of age.[62] In a controlled setting, use of an integrated model for screening was effective in diagnosing children before 36 months of age.[90] Original findings of behaviors suggesting the need for an intellectual evaluation included 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.[72] Earlier intervention is recommended when the early signs and symptoms of ASD are recognized.

It is difficult to determine if ASD is present in persons with severe to profound ID; therefore, a diagnosis is made in such cases when there are

qualitative deficits in social and communicative skills and the specific behaviors characteristic of ASD are present.[62] A key central difference between ID and ASD is that persons with ID 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.[89]

Although there are no definitive biologic markers for identifying individuals with ASD, a number of medical evaluations should occur at baseline, to assist in distinguishing the diagnosis as ASD and to rule out other disorders. Table e93-1 delineates the parameters to be considered in a medical evaluation for persons suspected of having ASD and the rationale for the assessment.

TABLE e93-1

Medical Screening for Individuals with Autism Spectrum Disorder

Parameter>	Rationale
Health, medical, behavioral, and developmental history	Perform initial screening or 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 ASD (receptive language deficits); most are normal
Heavy metal testing	Perform if there is a history of malnutrition, recurrent vomiting, early onset seizures, dysmorphic features, presence of ID or developmental delays
Genetic testing for karyotype, fragile X, Rett syndrome	Benefits family for genetic counseling purposes; evaluation of siblings, if applicable; review family history for three generations
Test for inborn errors of metabolism/metabolic testing	Indicated in those with a history of lethargy, recurrent vomiting, early seizures, dysmorphic or coarse facial features, ID
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 ASD alone or in the presence of developmental regression, particularly language
Neuroimaging	Evaluate neurologic findings that cannot be explained by the diagnosis of ASD alone; identify specific neuropathological changes associated with ASD, including brain volume

CBC, complete blood count; EEG, electroencephalograph.

Data from References 79, 91 and 135.

Those individuals with ASD and intelligence quotients (IQs) above 70 who use communicative language by ages 5 to 7 have the best prognoses.[89] Conversely, low IQ scores and failure to develop communicative language by age 5 years correlate with a poorer long-term prognosis.[89] Outcome studies in persons with ASD correlate IQ, particularly verbal IQ, with the ability to be employed and live independently.[91] Studies indicate that high-IQ children with ASD can make positive changes in communication and social domains more effectively over time. The areas less likely to improve are those related to ritualistic and repetitive behaviors.[92] Up to 80% of children diagnosed with ASD continued to experience marked impairment in social interactions as adults and mild-to-moderate ID was reported for approximately 30%.[93]

In addition to the core symptoms of ASD, many persons with this disorder exhibit other significant maladaptive behaviors, such as aggression toward

self and others. These behavioral issues can interfere with day-to-day activities and are challenging for the individual, families, and caregivers.[94]

TREATMENT

Desired Outcomes

5 Treatment goals in persons with a diagnosis of ASD are to maximize their ability to lead a full self-directed life through person-centered approaches to care and support. This includes addressing deficits in communication and social interaction using a structured approach and minimizing the impact of restricted behaviors (eg, stereotypies or repetition) appropriate to the level of intellectual ability, language development, and chronologic age. The multimodal treatment plan should address: (a) establishing realistic goals for educational efforts, (b) identifying the presence of behavioral target symptoms for intervention, (c) prioritizing target symptoms and comorbid conditions for intervention, (d) using specific methods of outcome monitoring of functional domains (eg, behavioral skills, adaptive skills, academic skills, social interaction skills, communication skills), and (e) monitoring for efficacy and potential adverse effects of medication (if used). The National Institutes of Health (NIH) suggests that evidence-based treatment strategies include the use of both psychoeducational therapies and medications.[95] An effective, well-designed, multimodal treatment plan that is consistently executed has the most potential to positively shape how an individual with ASD interacts with the environment and improve their quality of life and that of their families and caregivers.

6 After a thorough diagnostic evaluation, treatment planning for the individual with ASD is critical to assure consistency and efficacy of interventions. With the often-severe nature of the behavioral and adaptive problems, many potential treatment modalities lacking results have been proposed for persons with ASD. The two treatment approaches for ASD with evidence-based support and clinical consensus are behavioral/psychoeducational therapies and psychoactive medication intervention[72] as appropriate. All stakeholders (family, educators, caregivers, clinical professionals, and the patient) should be involved in the treatment planning process, and decisions should be evidence-based and individualized to the specific identified needs of the individual. The potential for communication deficits often limits self-reporting of psychopathology. A multifaceted approach to information gathering should include direct observation; interviews with patient, parents, family, caregivers, and teachers; and review of the medical record, including any behavioral rating scale information.

Nonpharmacologic Therapy

7 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. Services, such as occupational therapy, physical therapy, and speech pathology, are often integral aspects of an overall educational plan. Because of the pervasive need for sameness in routine, ongoing and consistent year-round educational programming is more effective than intermittent, episodic interventions. Effective language and communication training can lead to generalized improvements in social skills and repetitive behaviors, and thus positively impact other nonspecific maladaptive behavioral problems such as noncompliance, self-injury, and aggression.[72]

Intervention strategies, such as discrete trial training, improve challenging behaviors. Educational techniques include structuring the environment, family training, peer role modeling, and sensory integration to optimize environmental interactions.[72] Applied behavior analytic interventions have funding to support utilization by people with ASD.[94,96]

Pharmacologic Therapy

6 Evidence-based therapy for ASD is limited to the treatment of co-occurring behaviors or diagnosis, and not ASD itself.[72] Many of the studies of psychopharmacologic interventions in persons with ASD have methodologic shortcomings including problems in experimental design and sample size, poorly defined diagnostic criteria, and many clinical outcomes that were limited in duration or of dubious clinical significance. Among a number of scientifically unsupported treatments for ASD is the use of complementary and alternative medicine. According to a study of 540 families of children with ASD, the child/family had tried an average of seven complementary and alternative medicine therapies.[97] Elimination diets in which casein (from dairy products) and/or gluten (from wheat products) are excluded from the diet have no benefit. Other such purported therapies include omega-3 fatty acids and selected herbal remedies, specifically ginkgo biloba. However, controlled trials have no significant differences between omega-3 and ginkgo biloba supplementation compared to placebo.[98]

8 Current research on the neurobiologic basis of ASD is centered on the serotonergic, peptidergic, dopaminergic, and noradrenergic systems. This research has particular applications for insomnia in ASD, as the prevalence of sleep disorders has been reported to range from 44% to 83%.[99] Parents commonly rate sleep disturbance as a significant clinical issue. As with patients without ASD, it is important to determine the underlying etiology of the sleep problem. Behavioral interventions (eg, improved sleep hygiene, eliminating maladaptive sleep habits, and parental education) should be undertaken prior to implementing pharmacotherapy. No medication is approved by the FDA for pediatric insomnia. While controlled trial data are limited, there is support for the use, of melatonin as it has been reported to improve sleep, and specifically, result in shorter sleep onset latencies. When used in ASD, doses range from 0.75 to 6 mg and adverse effects are mild (eg, headaches, GI upset, dizziness).[100] Chapter 92, "Sleep Disorders" outlines the treatment of sleep disorders in greater detail.

9 Aggression to self and others and severe tantrums are a concern, particularly with adults with ASD. In addition to inclusion of nonpharmacologic interventions, pharmacotherapy is frequently utilized. Despite limited evidence-based support, psychoactive medications have been widely used to minimize the frequency and intensity of these behaviors. Clinicians must identify and carefully monitor specific behavioral target symptom response to avoid the practice of overprescribing psychoactive medications.

Antipsychotics

An association between dopamine dysregulation and increased aggression, including self-injury, consistent with animal models, has been proposed.[94] Such findings have led to the use of antipsychotic agents, that act as dopaminergic antagonists, to address aggression and SIB. The first-generation antipsychotic agent with highest short- and long-term safety and efficacy is haloperidol. Target behaviors included impaired learning, anger, mood lability, hyperactivity, and social withdrawal. Although antipsychotic treatment resulted greater improvement in the target behaviors compared with the placebo group, the risk for the development of dyskinesias is high, therefore the newer second-generation antipsychotics are preferred over first-generation agents.[101]

10 As few psychopharmacologic agents have been well studied in this population, and even fewer have received FDA approval, current research has focused on the second-generation antipsychotics. Off-label use of FDA-approved medications (ie, use of an approved medication 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; however, there is a relative lack of robust research in this area at the present time.

Aripiprazole and risperidone are FDA approved to treat the behavioral (eg, irritability) symptoms associated with ASD.[101,102] Both short- and long-term use of orally administered aripiprazole, dosage rang of 2 to 15 mg per day, was effective for irritability in pediatric patients with ASD. Aripiprazole related adverse medication reactions resolved with continued use.[103-106] Weight gain was reported during the first 3 to 6 months, plateauing thereafter.[103] Risperidone has the most evidence-based support for treating behavioral problems associated with ASD and is FDA-approved for treatment of SIB, aggression, temper tantrums, and irritability in children and adolescents with ASD.[72] The efficacy of risperidone in the treatment of irritability associated with ASD was established in several short-term (6-8 weeks), placebo-controlled trials in children and adolescents (aged 5-17 years) who met the DSM-IV criteria for ASD. Significant improvements in outcomes measures such as the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression - Change (CGI-C) scale were seen.[107,108] Short-term studies also have some success in reducing repetitive behavior, aggression, irritability, and overall behavioral symptoms in adults with ASD.[109] The use of olanzapine is supported by limited trial data in children and adolescents with ASD. Trial durations were generally short (6-8 weeks) with small numbers of participants. Positive results are generally reported in CGI; however, the significant weight gain and sedation noted these trials are important considerations in weighing risk versus potential benefit.[72] A post-hoc analysis of the health-related quality of life of pediatric patients receiving aripiprazole improved the scores compared to placebo in three of five subscales, including emotional, social, and cognitive functioning.[110] Aripiprazole reduces irritability, but its behavioral effects have not been examined adequately.[111]

The second-generation antipsychotic agents are less likely to elicit extrapyramidal adverse medication reactions than first-generation agents due to more potency at serotonin 2A (5-HT2A) receptors versus dopamine receptors. However, the second-generation agents have been implicated in weight gain in some persons with ASD.[72] The potential serum prolactin elevation related to risperidone use is of concern as this may lead to amenorrhea, galactorrhea, and osteoporosis in females and gynecomastia and sexual dysfunction in males. The minimum degree of prolactin elevation that is

clinically relevant is uncertain, as are the implications for long-term use in a pediatric population. If detected, strategies include evaluating the risk–benefit with continued use, reducing doses, or changing to another agent with less impact on prolactin. Clinicians must monitor for the evidence of potential risperidone-mediated prolactin elevations regardless of whether a prolactin level is obtained.[112] Additional monitoring recommendations for antipsychotic use and the monitoring of adverse effects can be found in Chapter 87 "Schizophrenia."

Selective Serotonin Reuptake Inhibitors

Serotonin synthesis differs between children diagnosed with ASD and children without this diagnosis as 5-hydroxytryptamine (5-HT) synthesis may peak at twice the adult level in developmentally normal children by age 5 years, whereas children with ASD have a more gradual developmental arc with a lower peak.[113] The use of selective serotonin reuptake inhibitors is often associated with a decrease in some of the core behavioral symptoms such as stereotypies, social withdrawal, and rigid adherence to routine. Citalopram, escitalopram, fluoxetine, and fluvoxamine have limited support for use of SSRIs to address behaviors of ASD.[113,114] There is no FDA-approved medication for the core symptoms of ASD. Prior to the inclusion of pharmacotherapy for behavior as a component of the plan, utilization of a multifaceted approach is recommended.[72]

Psychostimulants

ADHD is the most common comorbidity in people with ASD (28.2%).[72] Psychostimulants have been studied in persons with ASD to address hyperactivity, impulsivity, inattention, and ADHD. Pharmacologically these agents block the reuptake of dopamine and norepinephrine, which may support their use in ADHD as their use may correct dysfunction in the regulation of these catecholamines.[112] The largest and most rigorously controlled trial of methylphenidate involved 72 participants, with 74% having a primary diagnosis of ASD. In this placebo-controlled trial, methylphenidate was given in divided doses of 0.125, 0.25, and 0.5 mg/kg (morning and noon doses) with 16 participants not being able to tolerate the 0.5 mg/kg dose phase. All three doses performed better than placebo on improving the core symptoms of ADHD, with the medium dose performing better than the low dose according to the parent and teacher ratings.[115] The doses used in this trial were generally lower since the patients with ASD were unable to tolerate the higher doses commonly used in ADHD patients. In terms of adverse medication reactions, irritability and stereotypic behaviors, GI complains, and sleep disturbances are seen with the higher doses.[116] Another agent, atomoxetine, has been reported to significantly reduce hyperactivity in small trials with a moderate level of adverse effects similar to methylphenidate.[117] The treatment response to psychostimulants varies.[118] The α2-agonists, clonidine and guanfacine, have also been used to treat hyperactivity and agitation in persons with ASD because of their pharmacologic effects on noradrenergic release and transmission. Both agents have FDA approval for treating symptoms associated with ADHD; however, as with many psychoactive medications used in the ASD population, there is a lack of methodologically sound studies supporting use of these agents. Two trials reported positive outcomes with guanfacine when used for the targeted symptoms of inattentiveness and hyperactivity, with global improvements being noted in one.[118] Therefore, aggressive behavior, sleep disturbances, and anxiety may respond to α2 adrenergic receptor agonists with common adverse effects including drowsiness, fatigue, and decreased appetite (Table e93-2).[119] The response to methylphenidate and atomoxetine is less than what is typically observed in patients without ASD, while the response to guanfacine for hyperactivity was greater. On the other hand, adverse effects are more common for guanfacine, while atomoxetine may be better tolerated.[120]

TABLE e93-2

Common Psychotropic Medications Used in Down Syndrome and Austin Spectrum Disorders

Medication>	Indications	Target Symptoms	Common Adverse Medication Reactions
Second-Generation Antipsychotics			
• Risperidone • Aripiprazole	• Self-injurious behavior, aggression, temper tantrums, irritability • (Risperidone and aripiprazole approved for irritability in ASD)	• Irritability, aggression • Aberrant social behavior	• Sedation, drowsiness, medication-induced extrapyramidal reaction • Insomnia, fatigue, parkinsonian-like syndrome, headache • Anxiety, dizziness, drooling • Hyperprolactinemia, weight gain, increased appetite • Increased serum total and LDL cholesterol, triglycerides, glucose • Decreased HDL cholesterol • Vomiting, constipation, upper abdominal pain, nausea, urinary incontinence • Tremor, nasopharyngitis, cough, rhinorrhea, fever
Cognitive Enhancers			
• Memantine • Donepezil • Rivastigmine	Memory, cognition	Cognition	• Hypertension, hypotension • Dizziness, insomnia, confusion, headache, anxiety, depression, drowsiness, hallucination, pain, aggressive behavior, fatigue, back pain • Weight gain, weight loss (rivastigmine), diarrhea, constipation, vomiting, abdominal pain, urinary incontinence • Cough, dyspnea
Miscellaneous			
• Oxytocin • Vasopressin	• Aberrant social behavior • Social behavior, communication	• Emotion recognition • Eye gaze	Nasal discomfort (intranasal oxytocin), tiredness, irritability, diarrhea
Melatonin	Sleep disorder		Dizziness, enuresis, excessive daytime somnolence, headache, nausea, insomnia, nightmares, and transient depression
• Methylphenidate • Atomoxetine • Clonidine • Guanfacine	Treatment of attention-deficit/hyperactivity disorder (ADHD)	Hyperactivity, inattention	• Insomnia, headache, irritability • Decreased appetite, xerostomia, nausea, early morning awakening • Drowsiness and fatigue (clonidine, guanfacine)

Miscellaneous Agents

Vasopressin, which is thought to influence social behavior, is a closely related hormone to oxytocin. Physiologically the oxytocin and vasopressin receptors are highly expressed in the amygdala, hippocampus, and nucleus accumbens, and play a role in behaviors, bonding, and parental care.[121,122] Short-term studies of intravenous and intranasal administration of oxytocin showed decreased repetitive behaviors and enhanced social cognition in patients with ASD[123-126]; however, more recent work on intranasal oxytocin provides inconclusive results.[124] The medication balovaptan is an oral agent that inhibits vasopressin V1a from binding to receptors in the brain. Early studies showed the potential to improve social interaction and communication in patients with ASD.[126] However, a 2-year open-label extension study of balovaptan in adults with ASD was terminated early due to lack of efficacy.[127]

The current dearth of evidence-based psychopharmacologic and behavioral research in persons with ASD is being addressed by a network of NIH-funded research centers, including the research units of Pediatric Psychopharmacology, Centers for Programs of Excellence in Autism, and Studies to Advance Autism Research and Treatment. The mission of these units is to foster well-controlled, multicenter, behavioral, and psychopharmacologic intervention studies targeting behavioral symptoms in persons with ASD.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring the safety, efficacy, and tolerability of psychopharmacologic interventions in persons with ASD is imperative to minimize adverse medication-related sequelae and optimize desired therapeutic outcomes. Clinical investigators have used a variety of psychometric assessment instruments in attempts to measure changes in core symptoms such as communication impairment, restricted interests, repetitive, compulsive, ritualistic, or perseverative behaviors, irritability, hyperactivity, and variants of self-injurious behavior. While a comprehensive review of many of these instruments is beyond the scope of this chapter, the Aberrant Behavior Checklist consists of 54 items divided into five domains: irritability, hyperactivity, stereotypic behavior, lethargy, and inappropriate speech. This checklist was designed for assessment of behavioral changes in institutionalized individuals enrolled in pharmacotherapy trials; however, a community-based version is also available.[128,129] In addition, the Children's Yale-Brown Obsessive Compulsive Scale modified for PDDs is a validated scale sensitive to changes in repetitive behavior severity pretreatment and posttreatment.[130]

Intensive monitoring for medication-related adverse effects is critical for individuals with ASD, as self-reporting can be unreliable. Therefore, a caregiver-rated instrument, such as the Monitoring of Side Effects Scale, can be useful for this purpose as it 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.[131] 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 effect–specific scales such as those for akathisia (eg, Barnes Akathisia Scale), extrapyramidal effects (eg, Simpson-Angus Scale), or tardive dyskinesia (eg, Dyskinesia Identification System: Condensed User Scale [DISCUS]).[132-134]

Use of second-generation antipsychotics has been associated with increased risk of developing metabolic syndrome. Children, and adults, receiving these agents should be monitored for hyperglycemia, dyslipidemia, and weight gain in a manner consistent with the consensus guidelines suggested by the American Diabetes Association and the American Psychiatric Association. For monitoring guidelines, see Chapter 87, "Schizophrenia."

CONCLUSION

Psychotropic medications can be effective for the treatment of mental health conditions for people with IDD. Medication therapy must be coupled with other psychological therapies when a psychiatric disorder is confirmed by comprehensive assessment. Psychotropic medications should be used carefully for people with IDD, as there is increased risk of adverse medication interactions due to a high prevalence of polypharmacy, the patient having atypical responses to psychotropic therapy, and the inability of a person with IDD to describe the harmful or distressing effects of psychotropic therapy other than through changes in behavior.[129] One must remember that when assessing an individual with IDD who is exhibiting mental illness or challenging behaviors, physical-related problems may be underlying. For example, a person with minimal verbal communication may exhibit challenging behavior when experiencing pain from an underlying undetected tumor or broken bone. A complete examination and history taking, including information from caregivers who work with the person, is necessary in order to make an accurate diagnosis and recommendation for treatment.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ABC	Aberrant Behavior Checklist
AD	Alzheimer's disease
ADHD	attention-deficit/hyperactivity disorder
ASD	autism spectrum disorder
BAS	Barnes Akathisia Scale
CAM	complementary and alternative medicine
CBT	cognitive behavior therapy
CGI-C	Clinical Global Impression-Change
DD	developmental disability
DISCUS	Dyskinesia Identification System Condensed User Scale
DNA	Deoxyribonucleic acid
DS	Down syndrome
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECT	electroconvulsive therapy
EGCG	epigallocatechin-3-gallate
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GI	gastrointestinal
5-HT	5-hydroxytryptamine
5-HT_{2A}	serotonin_{2A}
ICF	International Classification of Functioning, Disability and Health scaling system
ID	intellectual disability
IDD	Intellectual Developmental Disabilities

IQ	intelligent quotient
NIH	National Institutes of Health
PDD-NOS	pervasive developmental disorder-not otherwise specified
SIB	self-injurious behavior
SIB	Severe Impairment Battery
SSRI	selective serotonin reuptake inhibitor

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SELF-ASSESSMENT QUESTIONS

1. Which of the following deficits associated with intellectual disabilities may mask signs of psychiatric disorders?
   A. Inattentiveness
   B. Functional adaptations related to stress management
   C. Syndrome-specific features such as hand-flapping or self-hugging
   D. Receptive language skills
2. Advanced age of which direct ancestor(s) is most frequently identified as a risk factor for Down syndrome?
   A. Maternal grandmother
   B. Paternal
   C. Maternal
   D. Combined maternal and paternal
3. MJ, a 39-year-old woman diagnosed with Down syndrome and mild-to-moderate intellectual impairment, presents to psychiatric clinic accompanied by her family. Her parents report she has become increasingly irritable over the past 6 months, more socially withdrawn, and lethargic. The family is interested in further assessment and possibly instituting therapy. Based on this information, which would you recommend at this point?
   A. Screen for a seizure disorder
   B. Screen for a cardiac event
   C. Screen for possible fractures
   D. Screen for hypothyroidism and depression/anxiety
4. A 5-year-old child experienced normal development until about 2 years of age when her parents noticed she did not talk as much as her peers and did not make good eye contact with her parents. As a toddler she played with her sister, but now prefers solitary play. Parents, teachers, and clinicians now suspect the child meets the criteria for diagnosis of ASD. Which feature would help confirm this diagnosis?
   A. Hand wringing
   B. Bruxism
   C. Temper tantrums
   D. Restricted preferences for only certain toys and/or foods, including marked preference for sameness
5. A colleague requests a consult for a 16-year-old patient with Down syndrome recently diagnosed with bipolar disorder and started on lithium. You

state that:

A. The evidence suggests no monitoring is needed.

B. A significant causal link exists between these comorbidities.

C. Closer thyroid monitoring may be needed in this patient.

D. Renal function may be impaired in persons with Down syndrome.

6. A child with a confirmed diagnosis of ASD is in your pediatric clinic. What is the most common neurological problem in children with a diagnosis of ASD?

A. Seizure disorder

B. Tourette disorder

C. Rett syndrome

D. Neurogenic scoliosis

7. The parent of a child with ASD complicated by extremely aggressive behaviors asks about a trial of risperidone for these challenging behaviors. Nonpharmacologic strategies have already been implemented with limited success. You discuss this potential medication therapy with the mother and explain that:

A. First-generation antipsychotic agents are less expensive and equally effective as second-generation agents.

B. Secretin may be a better therapeutic option for this child.

C. The parent should check for complementary and alternative medication options as these have strong support for efficacy.

D. Risperidone has the strongest evidence-based results in treating aggressive behaviors associated with ASD.

8. Early diagnosis and appropriate treatment are important for children with ASD in order to:

A. Promote maximal learning, improve behaviors/communications, and engage in recreation/social/occupational activities.

B. Implement pharmacotherapy and titrate the dose as quickly as possible.

C. Justify institutional placement for vocational training opportunities.

D. Enroll the parents and child in support groups and counseling.

9. Parents bring their 18-month-old child to your pediatric clinic. They mention the child does not enjoy playing with his/her siblings, has no interest in his/her parents, and has not begun to speak single words. What guidance should be given to these parents?

A. Refer the family to a developmental evaluation center for a multidisciplinary workup.

B. Minimize their concerns due to the young age of the child and reevaluate in 6 months.

C. Refer the family to a support group for ASD.

D. Discuss neuroimaging to rule out brain pathology or injury.

10. As part of a medical workup for a child with suspected ASD, which of the following is *not* commonly performed?

A. Detailed medical and developmental history

B. Lead or heavy metals testing, especially if pica is present

C. Genetic testing of parents and child

D. Electrocardiography at baseline and in 6 months

11. What clinical condition associated with personality and behavior changes may present in Down syndrome adults?

A. Hypothyroidism

B. Obsessive–compulsive disorder

C. Alzheimer disease

D. Megakaryoblastic leukemia

12. When conducting a face-to-face medication regimen review of a person who has Down syndrome and mild cognitive impairment, the clinician should:

A. Only review a written medication list and medical record since the caregivers will not be able to provide meaningful information.

B. Include the patient to the best of their ability in all lines of questioning.

C. Focus only on the psychotropic medication.

D. Educate only the caregivers when it appears that there is a deficit in understanding medication regimens.

13. A family physician asks you for a recommendation for a sleep agent for an adolescent patient who has autism spectrum disorder and is experiencing sleep problems. Which of the following is the most appropriate recommendation to make?

A. Start zolpidem, 5 mg every bedtime, increasing to 10 mg every bedtime after 2 weeks.

B. Have the patient exercise just before bedtime to induce fatigue.

C. Assess the patient's routine around bedtime to see if changes in activities can be made in an effort to produce a calming environment.

D. Start melatonin oral therapy immediately, as there is strong evidence that this intervention is the most effective intervention for insomnia for people with ASD.

14. Treatment goals in persons with a diagnosis of ASD are to:

A. Maximize their ability to lead a full self-directed life through person-centered approaches to care and support.

B. Completely eliminate repetitive speech patterns.

C. Increase the IQ of the patient.

D. Ensure the patient is prescribed at least one antipsychotic medication in order to prevent the development of new stereotypic symptoms.

15. Which of the following is *not* true regarding psychotropic medication regimens for people with IDD?

A. Medication regimens tend to be more complex.

B. Patients with IDD often rely on other people to manage their medications for them.

C. Patients with IDD have multiple medical problems which lead to polypharmacy.

D. A person with IDD can usually describe harmful or distressing effects of psychotropic therapy.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** All answers may contribute to the masking of psychiatric disorders in people who have IDD. Diagnostic overshadowing is where the clinician assumes a sign or symptom is related to the IDD condition when instead it may actually be the result of an underlying mental illness. People who have IDD may not be able to communicate or that the ability to cope with stress-related concerns or anxiety, and instead will "act out" in behaviors that may mimic those of mental illness. (Refer to the "Epidemiology" and "Challenging/Self Injurious Behavior" sections.)

2. **C.** Maternal age is the most consistently identified risk factor for Down syndrome, although some studies also implicate paternal age as well. (Refer to the "Down Syndrome" section.)

3. **D.** Hypothyroidism is a common comorbidity in persons with Down syndrome. Anxiety and depression are also seen. As a work-up for Alzheimer's dementia, examining other causes for changes in behavior are warranted. (Refer to the "Alzheimer's Disease in Down Syndrome" section.)

4. **D.** There are a number of social and behavioral observations that parents and teachers may see in a child who is suspected of having ASD. Focusing excessive attention on specific objects or toys at the expense of interacting with other toys in a child's environment is one example. (Refer to "Clinical Presentation" in the "Autism Spectrum Disorder" section.)

5. **C.** People with Down syndrome have a higher likelihood of experiencing hypothyroidism compared to the general population. (Refer to the "Down Syndrome/Clinical Presentation" section.)

6. **A.** Prevalence of seizure disorders in people with ASD is between 2% and 21% and is higher than the general population. (Refer to the "Clinical Presentation" section.)

7. **D.** Of all the first- and second-generation antipsychotic agents, risperidone has the strongest support for the use for controlling aggressive and challenging behaviors in pediatric and adult patients who have ASD. (Refer to "Antipsychotics" in the "Autism Spectrum Disorder" section.)

8. **A.** Early diagnosis of ASD is essential to be able to engage the patient in the evidence-based behavioral programs. Patients who initiated behavioral programs early, as well as connecting families to support services, can lead to improved outcomes. (Refer to "Nonpharmacological Therapy" in the "Autism Spectrum Disorder" section.)

9. **A.** Multidisciplinary practices that include pediatricians, social workers, psychologists, and behavioral specialists can identify treatment options for the patient and their family. (Refer to the "Clinical Presentation" section.)

10. **D.** Causes of ASD are still relatively unknown but many are hypothesized. As well, other childhood medical conditions may have similar symptoms as seen with ASD. Ruling out other causes for symptoms is important to differentiate various diagnoses and to treat the causes once identified. (Refer to the "Autism Spectrum Disorder," Table e93-1.)

11. **C.** Adults with Down syndrome have a higher likelihood of developing Alzheimer disease compared to the general population. Changes in behavior, decreased participation in normal activities, and increased irritability are hallmarks to watch for. (Refer to the "Alzheimer's Disease in Down Syndrome" section.)

12. **B.** Many patients who have mild-to-moderate cognitive impairment are able to provide meaningful information about their medication regimens when asked in an appropriate way. (Refer to the "Patient Care Process" section.)

13. **C.** Sleep disorders are common for people who have ASD. Initially, clinicians should inquire about the patient's activities around bedtime, to see if changes can be made to reduce stress or activation. Medications, such as melatonin, should be tried only after nonpharmacological interventions have failed. (Refer to "Pharmacologic Therapy" in the "Autism Spectrum Disorder" section, Table e93-2.)

14. **A.** Interventions for a person with ASD should be based on their functional limitations and the patient and caregivers goals and aspirations, using a multidisciplinary team to create a plan that is continually reviewed and updated as the patient matures. (Refer to "Treatment" and "Desired Outcomes" sections in the "the Autism Spectrum Disorder" section.)

15. **D.** Psychotropic medications should be used carefully for people with IDD, due to polypharmacy, atypical responses to psychotropic therapy, and

the inability for a person with IDD to describe the harmful or distressing effects of psychotropic therapy other than through changes in behavior. (Refer to the "Epidemiology" section.)