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Autism and Its Treatment: A Primer for Pharmacists

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Goal. The goal of this lesson is to explain autism with focus on its pathogenesis, clinical characteristics and confirmation, and treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. recognize historical events concerning autism, and differentiate each component of the autism spectrum disorders from one another;
2. select important principles that characterize autism and the principles that govern its clinical confirmation and management; and
3. identify specific nonpharmacologic and pharmacologic measures that are reported to modify signs and symptoms of autism.

Autism (autistic disorder) is a complex, chronic and serious neurodevelopmental disorder that affects normal functioning of the brain, impacting development in the areas of social interaction and communication skills. The most common of the pervasive developmental disorders, autism affects an estimated one in 150 births in the United States. With the number growing at a startling rate of 10 to 17 percent per year, its prevalence could reach four million Americans within a decade. Occurring in all racial, ethnic and socioeconomic groups, autism is four times more likely to occur in males than in females. Additional information on autism can be found in the online resources listed in Table 1.

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Background

In 1943, child psychiatrist Leo Kanner of the Johns Hopkins Hospital published the first description of "autistic disturbances of affective contact." Kanner thus introduced the term *infantile autism*, or *autism* into the English language, which defined three symptom patterns: (1) abnormal development of social reciprocity; (2) failure to use language for communication; and (3) desire for sameness, as seen in repetitive rituals or intense circumscribed interests – symptoms that were later termed *Kanner's triad*.

About this same time, Austrian pediatrician Hans Asperger, based on his study of 400 children, described a milder form of the disorder that became known as *Asperger's Disorder* (*Asperger Syndrome*).

Autism is listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), the primary diagnostic reference for mental health professionals in the United States. It is one of the five pervasive developmental disorders (PDDs), more commonly referred to as autism spectrum disorders (ASDs). Each disorder is characterized by varying degrees of impairment in social interactions, communication skills and restricted, repetitive and stereotyped patterns of behavior. (Table 2) It is not uncommon for more than one of these disorders to coexist in the same family.

Table 1
Representative sources for information on autism

The American Academy of Pediatrics	www.aap.org
The Autism Society of America	www.autism-society.org
Autism Speaks, Inc.	www.autismspeaks.org
First Signs, Inc.	www.firstsigns.org
The Organization for Autism Research	www.researchautism.org
National Library of Medicine and the National Institutes of Health	www.nlm.nih.gov/medlineplus/print/autism.html
National Institute of Mental Health	www.nimh.nih.gov
National Institute of Child Health and Human Development	www.nichd.nih.gov

Table 2
Major characteristics of pervasive developmental disorders

Disorder	Age at onset (months)	Major characteristics
AD	<36	social and communication skills impairment; stereotyped, repetitive/restrictive behavior and interests
PDD-NOS	variable	symptoms not meeting other diagnoses; frequently a milder form of autism; also known as atypical autism
Asperger's disorder	>36	impaired social interactions and restricted interests; delay in motor skills; preservation of early language skills; limited conversational abilities
CDD	>24	normal early development followed by deterioration in social skills, language, behavior, bowel/bladder control and play
Rett syndrome	5-30	progressive developmental disorder with normal early infancy, followed by loss of fine and gross motor skills, language skills, interests, and social interactions; appearance of characteristic hand-wringing movement and muscle-wasting

AD = autistic disorder; PDD-NOS = pervasive developmental disorder-not otherwise specified; CDD = childhood disintegrative disorder

*Adapted from Stachnik JM, Nunn-Thompson C. Ann Pharmacother. 2007.41;626-*634

Pathogenesis

Although there is no known single cause for autism, it is generally accepted that it follows some abnormality in brain structure or function. Brain scans reveal differences in the shape and structure of the brain in children with autism compared to those without.

Research is ongoing in investigating possible links between heredity, genetics and medical pathology. There appears to be a pattern of autism or related neurological disabilities in many families.

Medical researchers have identified a variation in a gene that may increase the risk for developing autism, especially when the variant is inherited from mothers rather than fathers. The gene, CNTNAP2, encodes a protein that facilitates communication between brain cells through chemical signals and appears to play a role in brain cell development. Inheriting the gene variant does not imply that a child will inevitably develop autism; rather, it means that a child may be more vulnerable to developing the disease.

Other research suggests that a cluster of unstable genes may interfere with normal brain development, resulting in autism. Pregnancy or delivery problems and environmental factors (e.g., viral infections, metabolic imbalances and exposure to environmental chemicals during pregnancy) are also being studied.

Is there a causative role for vaccines? Many studies over the years have looked at the possibility that vaccines are a cause of autism. Autistic characteristics have been described in some children within a few weeks of receiving a vaccine. Until 1999, vaccines intended for infants to protect them against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B contained thimerosal (a mercury-based preservative). Today, with exception of some influenza vaccines, none of the preparations used in the United States to protect preschool-aged children against 12 infectious diseases contain thimerosal. The MMR (measles, mumps, rubella) vaccine, varicella (chickenpox), inactivated polio, and pneumococcal conjugate vaccines do not and never did contain thimerosal.

The U.S. Institute of Medicine (IOM) conducted a thorough review on the issue of identifying a possible link between thimerosal and autism. The IOM report, released in May 2004, stated that there was no link. At this time, there is no conclusive scientific evidence that any component of a vaccine or combination of vaccines causes autism.

Characteristics

Characteristics (i.e., signs/symptoms) of autism may be evident as early as four months of age. In a few cases, after developing normally, a child regresses into autism. Clinically, neurological abnormalities usually dominate the symptomatology. At the same time, it is emphatically true that intelligence diversity is a major aspect of autism. It has been reported that while approximately three-fourths of patients with autism may be mentally retarded, the IQs of persons with autism may range from severe impairment to intellectually gifted.

Impaired social interaction is the hallmark feature of autism. Table 3 lists common characteristics.

Parents are usually the first to notice symptoms of autism. Early in infancy, a baby with autism may be unresponsive to people or focus intently on one item to the exclusion of others for long periods of time. A child with autism may appear to develop normally for a period, only to withdraw and become indifferent to social interaction.

They may fail to respond to their name and often avoid eye contact with other people. They have difficulty interpreting what others are feeling because they don't understand social cues, such as tone of voice or facial expressions, and they don't watch other people's faces for clues about appropri-

ate behavior. They lack empathy toward others.

Many children with autism engage in repetitive movements such as rocking their head or torso and twirling their hair between fingers, or in self-abusive behavior such as biting or head-banging. They also tend to start vocalizing later than children without autism. Some speak in a high-pitched, or flat, robot-like voice, or in "sing-song" fashion (regular or monotonous rising and falling intonation) about a narrow range of favorite topics.

Many children with autism have an increased threshold to pain, but are abnormally sensitive to sound, touch, or other sensory stimulation. These reactions may contribute to behavioral symptoms such as resistance to being cuddled or hugged.

Children with autism appear to be at higher risk for certain comorbid (concomitant but unrelated) conditions, including fragile X syndrome (the most common inherited form of mental retardation) and tuberous sclerosis (a rare, genetic disorder that causes benign tumor growth in the brain and other vital organs), as well as epileptic seizures, Tourette syndrome (characterized by presence of multiple physical [motor] tics and at least one vocal [phonic] tic), learning disabilities, and attention deficit disorder. For reasons that remain unclear, about one-third of children with autism develop epilepsy by the time they reach adulthood. While persons with schizophrenia may show autistic-like behavior, symptoms usually do not appear until their late teens or early adulthood. Most persons with schizophrenia also experience hallucinations and delusions, neither of which are associated with autism.

Autism symptoms often improve with treatment and with age. Some autistic children can lead normal or near-normal lives as they grow older. Children whose language skills regress early in life, usually before three years of age, appear to be at risk of developing epilepsy or seizure-like brain activity. Some children with autism may become depressed or experience behavioral problems during adolescence.

Persons with autism score consistently low on instruments that measure life skills. The life outcomes of autistic adults range from complete dependence on others to (rarely) successful employment. People with autism typically die early, with death most often coming from seizures, nervous system dysfunction, drowning or suffocation (at a rate exceeding three times the general population). As mentioned earlier, epilepsy occurs in at least one-third of persons with autism. The death rate due to epilepsy is approximately 24 times higher than that of epileptic patients without autism.

Confirmation of Autism

There is no medical test for autism. Physicians rely on a core group of behaviors to diagnose autism:

- difficulty in making friends with peers;
- inability to initiate or sustain conversation with others;
- impairment or absence of imaginative and social interaction;
- unusual, stereotyped or repetitive use of language;
- patterns of interest that are abnormal in intensity or focus;
- preoccupation with a particular object or subject; and
- rigid adherence to established routines or rituals.

While some screening instruments rely solely on parental (or caregiver's) observations, others rely on a combination of notes from both parent and physician. Since autism is a complex disorder, a comprehensive evaluation requires a multidisciplinary team including a neurologist, psychiatrist, psychologist, speech therapist and other professionals who have experience in diagnosing children with ASDs. Team members will conduct a thorough neurological assessment and in-depth cognitive and language testing.

Autism can often be detected as early as 18 months. Increases in the number of autism cases in the United States may be the result of improved diagnosis and changes in diagnostic criteria.

Table 3
Common characteristics of persons with autism

A child or adult with autism might:
- not play "pretend" games
- not look at objects when another person points at them
- not have an interest in others
- avoid eye contact
- want to be alone
- have trouble understanding other people's feelings or talking about their own feelings
- prefer not to be held or cuddled
- appear to be unaware when other people talk to them but respond to other sounds
- be very interested in people, but not know how to relate to them
- repeat or echo words or phrases
- have trouble expressing their needs using words or motions
- repeat actions over and over
- have trouble adapting to a changing routine
- have unusual reactions to the way things smell, taste, look, feel or sound
- lose skills they once mastered

Adapted from www.cdc.gov/ncbddd/autism/actearly/autism.html

Differential Diagnosis. Children with some symptoms suggestive of autism, but neither qualitatively nor quantitatively sufficient to permit a diagnosis of classical autism, may be diagnosed with pervasive developmental disorder-not otherwise specified (PDD-NOS) (Table 2). Children with autistic behaviors whose language skills are well developed may be diagnosed with Asperger's disorder. Children who develop normally, and then suddenly deteriorate between three and 10 years of age and show marked autistic behaviors, may be diagnosed with childhood disintegrative disorder (CDD). Girls with autistic symptoms may be suffering from Rett syndrome, a gender-linked genetic disorder characterized by social withdrawal,

regressed language skills and hand wringing.

Treatment

Although treatment has improved greatly over the past several decades, there is neither a cure for autism nor single approach to therapy. The primary goals are to minimize the core features and associated deficits, maximize functional independence and quality of life, and alleviate family distress. Options may include behavioral and communication measures, drug therapies and complementary approaches.

Behavioral and Communication Measures. Numerous programs target the range of behavioral, social and language difficulties characteristic of autism. Some focus on reducing problem behaviors and teaching new skills. Others focus on teaching children how to communicate more effectively with other people or how to act appropriately in social situations.

Drug Therapies. At present, there is no medication that directly improves the core signs of autism. However, some can help control individual symptoms. Agents most commonly employed in autism include antidepressants (especially SSRIs), used in 20 to 25 percent of patients; neuroleptics (especially second-generation antipsychotics), 10 to 15 percent; stimulants, 10 to 15 percent; alpha agonists, 10 percent; and anticonvulsants, 5 to 10 percent.

Risperidone. The FDA approved risperidone (Risperdal) for the symptomatic treatment of irritability in autistic children and adolescents. The targeted behaviors under the general heading of irritability include aggression, deliberate self-injury, temper tantrums and quickly changing moods. No restrictions on prescribing or use in autism have been put into place to-date.

Risperidone's effectiveness in the symptomatic treatment of irritability associated with pediatric autistic disorders was established in two eight-week placebo-controlled trials in 156 patients aged five to 16 years of age. Outcomes demonstrated that children on risperidone achieved significantly improved scores for specific behavioral symptoms of autism compared to children on placebo. The most common side effects included drowsiness, constipation, fatigue and weight gain.

While efficacy has been demonstrated, concern remains about the misuse potential of risperidone and other antipsychotic drugs as a form of long-term chemical sedation, particularly with the most intellectually disabled children who may be the most likely to experience adverse drug effects. The overwhelming view, however, is that if antipsychotic drugs are used appropriately, they can have a positive role in the management of aggression associated with autism.

Complementary Approaches. In the absence of specific medical interventions for autism, parents and some healthcare professionals may choose complementary (i.e., alternative) therapies, such as art or music therapy; dietary restrictions including the elimination of gluten, sugar, chocolate, preservatives and food coloring; vitamin and mineral supplements; herbal remedies; or sensory integration, which focuses on reducing a child's hypersensitivity to touch or sound. Almost one-third of autistic children regularly receive a complementary therapy. Various surveys indicate that only 36 to 62 percent of caregivers who treated their autistic children with complementary therapies had informed the child's primary care physician.

Parents and caregivers should be encouraged to seek additional information when they encounter claims such as:

- treatments based on overly simplified scientific theories, and those supported primarily by case reports or anecdotal data rather than carefully designed studies;
- therapies claimed to be effective for multiple different, unrelated conditions or symptoms;
- claims that children will respond dramatically and some will be cured; and
- treatments that are said to have no potential or reported adverse effects.

Early Treatment. Individuals with autism won't outgrow it, but they can learn to function within the confines of the disorder, especially if treatment begins early. Early intervention is defined as treatment provided to children from birth to age three years. Research has clearly shown that early treatment, which consists of intensive, individualized behavioral interventions, can have a dramatic impact on reducing the symptoms of autism. Sadly, it is estimated that only 50 percent of autistic children are diagnosed before kindergarten.

Summary and Conclusions

Autism is a lifelong neurobiologic disorder that adversely affects quality of life. Early diagnosis of autism is often elusive. Its imprint on afflicted young people is so unique that the course of the disorder is difficult to predict in individual patients. In view of anticipated patterns of earlier identification and more proactive treatment of autism in years to come, the burden of autism on the health care system will continue to increase.

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continuing education quiz

Autism and Its Treatment: A Primer for Pharmacists

1. In the U.S., autism affects an estimated one in:
   a. 150 births.
   b. 1500 births.
   c. 15,000 births.
   d. 150,000 births.

2. The term *autism* has been defined as all of the following symptom patterns EXCEPT:
   a. abnormal development of social reciprocity.
   b. failure to use language for communication.
   c. desire for sameness.
   d. inability to perform mathematical tasks.

3. According to the Table listing *Major characteristics of pervasive developmental disorders*, autistic disorder has an onset of:
   a. <12 months of age.
   b. <24 months of age.
   c. <36 months of age.
   d. <48 months of age.

4. The U.S. Institute of Medicine has stated that:
   a. there is a link between thimerosal and autism.
   b. there is no link between thimerosal and autism.

5. It has been reported that approximately three-fourths of patients with autism may be:
   a. intellectually gifted.
   b. mentally retarded.

6. By the time they reach adulthood, about one-third of children with autism develop:
   a. schizophrenia.
   b. hallucinations.
   c. epilepsy.
   d. delusions.

7. All of the following are included in the core group of behaviors physicians use to diagnose autism EXCEPT:
   a. difficulty feeding and dressing oneself.
   b. inability to sustain conversation with others.
   c. preoccupation with a particular object.
   d. rigid adherence to established routines.

8. Girls with some autistic symptoms who also exhibit social withdrawal, regressed language skills, and hand wringing are most likely suffering from:
   a. Asperger's disorder.
   b. childhood disintegrative disorder.
   c. pervasive developmental disorder not otherwise specified.
   d. Rett syndrome.

9. The most common therapeutic agents employed to treat autism are the:
   a. neuroleptics.
   b. anticonvulsants.
   c. stimulants.
   d. antidepressants.

10. Common characteristics of persons with autism include all of the following EXCEPT:
   a. avoiding eye contact.
   b. begging to be held or cuddled.
   c. having trouble adapting to a changing routine.
   d. repeating actions over and over.

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