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Autism

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SUMMARY

Autism is truly a "spectrum" of disorders. A key theme in our understanding of

ASD centers on the tremendous heterogeneity, or variability, in the clinical presentation. This heterogeneity likely reflects the fact that many different neurobiological and developmental abnormalities can lead to ASD. No single brain region or genetic mutation is consistently implicated in the disorder. Rather, a variety of genetic and biological factors contribute to the development of ASD. This clinical variability can make treatment challenging as children may respond differently to various interventions. While there is not a gold standard treatment for ASD, the National Academy of Sciences recommends that all children with ASD receive intensive (minimum 25 hours/week) autism-directed behavioral and educational treatments. Additionally, two medications, risperidone and Arapiprazole, have been approved by the Food and Drug Administration (FDA) for treatment of "irritability" in ASD, with ongoing research on several other medications for symptoms associated with ASD. While there is no cure for ASD, current behavioral and medical treatments can be very effective in managing symptoms and improving daily function in children with ASD.

DESCRIPTION/SYMPTOMS

Diagnosis is based on DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) — see figure 1

ASD is a disorder of social behavior and communication.The clinical diagnosis is made using the Diagnostic and Statistics Manual (DSM). This manual is the standard classification of mental disorders used by health professionals. In the newest DSM, the 5th edition (DSM-5),published in May 2013, subtypes of autism were merged into one umbrella term of autism spectrum disorder (for details see section on Diagnostic Standards).

In DSM-5, ASD is placed in the chapter of neurodevelopmental disorders. Neurodevelopmental disorders are a group of conditions that present early in development, often in infancy, and reflect abnormal brain development. According to DSM-5, to meet criteria for ASD, a child must demonstrate:

1. "persistent deficits in social communication and social interaction across multiple contexts," and
2. "restricted, repetitive patterns of behavior, interests or activities"

Figure 1

DSM-5 Criteria for Autism Spectrum Disorder (APA, 2013)

Criterion A: Social communication impairment

Deficits in:

1. Social-emotional reciprocity
2. Nonverbal communication
3. Development, maintenance and understanding of relationships

Criterion B: Restricted, repetitive patterns of behavior, interests or activities

1. Stereotyped or repetitive motor movements, use of objects, or speech
2. Insistence on sameness
3. Abnormally intense restricted, fixated interests
4. Over or under reactivity to sensory input (i.e. taste, touch, sound) or unusual interest in sensory aspects of the environment

Criterion C: Symptoms must be present in early developmental period

Criterion D: Symptoms must cause significant functional impairment

Criterion E: Symptoms not better explained by intellectual disability or global developmental delay.

Severity of symptoms in each of the two areas is based on the level of support needed by the individual to function. These symptoms must be present from early childhood and limit or impair everyday functioning.

CRITERION A: SOCIAL COMMUNICATION IMPAIRMENT

In earlier versions of DSM, the social deficits and communication impairment were considered two separate categories within the autism diagnosis. However, the new diagnostic standard appreciates the interrelatedness of social function and communication and, therefore, in DSM-5 the two were combined into one criterion of "social communication deficits." Children with ASD demonstrate deficits in social-emotional reciprocity. For instance, they often are limited in their ability to initiate social interactions or to share their thoughts and feelings with others. Several studies have demonstrated deficits in empathy. Empathy is defined as the capacity to understand and share another person's experiences or emotions. In other words, the ability to "put yourself in someone else's shoes." Additionally, children with ASD may demonstrate language that is somewhat one-sided. For example, they may narrate events or speak in long monologues without making efforts to engage the other person in conversation or to listen to what the other person is saying.

Children also struggle with non-verbal communication. For example, they show either limited or abnormal eye contact, gestures, facial expressions and use of body language when interacting with others. The difficultly in developing and maintaining relationships can be seen in young children by their lack of social, reciprocal or imaginative play and, in later childhood, through a lack of flexibility in their play based on others' interests. Children may prefer to play alone or become very focused on the objects/toys with which they are playing. As children become older, they may have an interest in establishing a friendship, but they may find it difficult to understand how exactly to start or maintain a friendship.

CRITERION B: REPETITIVE AND RESTRICTED PATTERNS OF BEHAVIOR, INTEREST OR ACTIVITIES

Stereotyped and repetitive behaviors include:

- simple motor mannerisms (i.e. hand flapping)
- repetitive use of objects (i.e. flicking a light switch on and off)
- repetitive speech (i.e. reciting lines from a favorite song or television program)

Restricted patterns of behaviors include insistence of sameness, with difficulty in tolerating changes in routines. For instance, if the driving route to school is changed because of traffic, a child with ASD may become very agitated or frustrated. Another child may become very fixated on certain objects or activities and not only refuse to try new things, but become quite upset if forced to change.These restricted patterns of behavior are often seen in play, when children are unable to explore novel or imaginative ways to play with toys or other children, rather, they continue to play repetitively in a stereotyped way.

New to DSM-5 is the inclusion, within criterion B, of sensory processing abnormalities. Children with ASD may show evidence of increased (hyper-) or decreased (hypo-)sensitivity to certain sensory inputs, such as taste, smell or touch. For instance, a child may dislike the texture of crunchy foods and refuse to eat anything that is not soft or pureed. Another child may seem to not feel pain and will run into walls or bang his head without any distress. The term “sensory integration disorder,” used widely by occupational therapists, is not a formal clinical diagnosis in DSM-5. The term is considered somewhat descriptive rather than diagnostic and it reflects the observed sensory processing abnormalities found in many children with ASD, which are now included in DSM-5.

EARLY SIGNS

A formal diagnosis of ASD is usually not made before age 2, namely because children need to have reached a level of development at which they can show the impairments characterizing ASD, such as verbal or non-verbal communication, or play. However, many recent studies have tried to identify early signs of ASD in the first two years of life, with the ultimate goal of initiating interventions that may prevent ASD or at least improve the developmental trajectories of children with ASD. Two study designs are used to identify early signs: retrospective and prospective. In retrospective studies, information about a child’s early development is gathered through analysis of home videos or through questionnaires and reports about the child’s early history. In prospective studies, infants at high risk for ASD (usually infants who have an older sibling with ASD, or “infant siblings”) are followed from early infancy at repeated time points using a variety of measures, both behavioral and brain-based. Both retrospective and prospective studies have identified abnormal behaviors in children with ASD in the second year of life. Specific behavioral signs include:

- reduced response to name
- reduced social orienting
- repetitive behaviors
- abnormal use of objects

- problems with emotional regulation
- language delay
- motor delay

Because behavior is more limited in the first year of life, several prospective studies have attempted to define brain-based markers of ASD using Electroencephalography (EEG) or magnetic resonance imaging (MRI). Many of these studies are ongoing, but several have identified differences in brain activity between infants at high risk (infant siblings) and infants at low risk for ASD. No reliable markers have been identified that predict an ASD diagnosis. Most recently, a promising study using eye-tracking technology to measure infants' attention to faces found that infants who later developed ASD demonstrated a decline in their attention to the eyes from age 2 to 6 months.

EPIDEMIOLOGY

ASD is one of the world's most common developmental disabilities. According to the most recent estimates from the Centers for Disease Control (CDC), ASD affects 1 in68 children across the country. Because it is 4 times more common in boys, ASD affects 1 in 42 boys. Studies in other parts of the world, such as Asia and Europe, also have identified rates of ASD of about 1%. The prevalence of autism has increased over the last two decades. This increase largely, although not entirely, reflects the increased awareness about ASD, resulting in more accurate diagnoses of children and the diagnosis of children with milder impairments.

The high rates of ASD have important public health implications. For instance, the medical cost of raising a child with ASD is approximately 5 times higher than a healthy child, with the average medical cost for a Medicaid-enrolled child with ASD being just over $10,000/year. An additional $50,000/year for intensive behavioral interventions is estimated.

SEX BIAS

Like many childhood developmental and psychiatric disorders, ASD has a strong male predominance. There are two primary theories about the cause of this uneven distribution. (1) First, there is a diagnostic bias because boys tend to have more "externalizing" and disruptive symptoms, such as hyperactivity or aggression. These behaviors may lead to earlier referrals to specialists for diagnosis. Girls, in contrast, exhibit more "internalizing" symptoms, such as anxiety and depression. Because girls do not act out, their diagnosis can be delayed. (2) A second well-studied theory centers on sex-specific differences that may influence the way the brain is affected by the same genetic mutations. This theory is also referred to as the "female protective effect." It suggests that specific biological factors may protect females from developing a full clinical diagnosis of ASD. Females may have a higher threshold for reaching functional impairment and meeting criteria for a clinical diagnosis.

PHYSICAL ABNORMALITIES

There are no physical abnormalities commonly associated with ASD. Increased head size (macrocephaly) in early development has been found in a subset of children with ASD. Many of these children have genetic mutations that are

associated with macrocephaly. Additionally, several genetic syndromes associated with ASD — such as Tuberous Sclerosis Complex (TSC) — have characteristic physical abnormalities that help make their diagnosis. For instance, a physical examination of children with TSC may reveal:

- hypomelanotic macules (light spots on the skin)
- shagreen patches (leathery patches of skin, usually on the lower back)
- angiofibromas (small reddish brown spots on the side of nose and cheeks)
- periungual fibromas (thick growths of skin near the nail beds)

Many children with TSC have cardiac tumors known as rhabdomyomas that are diagnosed on perinatal ultrasound and facilitate the early diagnosis of TSC. In fact, this prenatal diagnosis makes TSC a promising high-risk group to study for early markers of ASD. Several studies are currently following these infants longitudinally or over time.

CAUSATION

There is no single cause of ASD, just as there is no single clinical presentation of ASD. Over the last decade, through collaborative studies of thousands of children with ASD, scientists have found several rare mutations, or changes, in genes that likely contribute to the development of ASD. Currently, more than 20% of children with ASD have an identified gene mutation. This number will likely grow over time with advances in technology used for genetic testing. Some known single gene disorders associated with ASD, include:

- TSC
- Fragile X
- Rett syndrome
- Neurofibromatosis

Other syndromes defined by having either a deletion or duplication of a small chromosomal region (known as copy number variants), include:

- Phelan McDermid syndrome (22q13 deletion)
- Velo-cardio-facial syndrome (22q11 deletion)
- 15q duplication syndrome
- 16p11 duplications and deletions

Some of these genetic mutations are inherited from a parent, but others are “de novo” or new mutations that occur in the child.

Most cases of ASD appear to result from a combination of these ASD risk genes and environmental factors influencing early brain development. These environmental factors are somewhat still unknown, but include:

- advanced parental age at time of conception (both mom and dad)
- maternal illness during pregnancy
- maternal alcohol or drug use
- difficulties during the birthing process that lead to reduced oxygen to the baby’s brain

It must be emphasized that these factors alone do not cause ASD; rather in combination with certain genetic mutations,they greatly increase the risk of developing ASD.

Over the years, there have been concerns that ASD may be caused by the

vaccines given to children in infancy and early childhood. One ingredient used as a preservative of vaccines, called thimerisol, has been the subject of particular concern. Thimerisol contains mercury which, in large doses, can be toxic to the brain. In 2001, thimerisol was removed or reduced to trace amounts in all vaccines administered to children under age 6, except one type of influenza vaccine (which now also has a thimerisol-free alternative). Several population-wide studies examining the relationship between rates of ASD and vaccine use have found no association between ASD and vaccines. A comprehensive scientific review performed by the Institute of Medicine (IOM) in 2004 concluded that "the evidence favors rejection of a causal relationship between thimerisol-containing vaccines and autism." The Centers for Disease Control (CDC) supported this conclusion. Therefore, both the CDC and IOM agree that the vaccines administered to infants are generally safe, with serious adverse events a rare occurrence. See the CDC website for details.

ADDITIONAL CONCERNS/COMPLICATIONS

INTELLECTUAL DISABILITY

ASD is highly associated with intellectual disability (ID), which is characterized by deficits in cognitive and adaptive skills. Approximately 70% of children with ASD have intellectual disability, both in verbal and non-verbal IQ.Although the level of intellectual disability can vary from mild to profound, most cases tend to be in the moderate/severe range. In those children with both ASD and Intellectual disability, other clinical problems include:

- deficits in adaptive behavior (activities that are important for day-to-day functioning)
- aggressive or challenging behaviors (such as self-injury)
- psychiatric disorders, such as anxiety or depression
- neurologic comorbidities, such as epilepsy (discussed below)
- genetic syndromes associated with ASD

LANGUAGE IMPAIRMENT

The language impairment in ASD ranges from subtle problems in the appropriate use of language in a social context to a complete lack of spoken language. By the time they enter primary school, up to 75% of all children with ASD will have some words, and at least 50% will be able to use phrased speech. Several studies have shown that "useful speech by age 5" consistently predicts better social and adaptive functioning later in life. Therefore, language function is one of the primary targets of early interventions. It is currently estimated that 25-30% of children with ASD remain minimally verbal, even after receiving years of interventions. Researchers are working to define predictors of language gain in young children with ASD using both behavioral and brain based techniques. Factors that are associated with later language ability include:

- oral motor skills
- imitation of sounds
- response to joint attention
- nonverbal cognitive abilities

EPILEPSY

Epilepsy is defined as the presence of more than one unprovoked seizure. Approximately 30% of individuals with ASD have epilepsy, but reported rates vary widely (6-50%) based on the samples studied. Most studies find two peak incidences, one in early childhood and the second in adolescence. Risk factors for epilepsy in ASD include:

- intellectual disability
- specific genetic syndromes (such as TSC, Dup15q mutations)
- female sex

There is no specific epilepsy syndrome associated with ASD, and all seizure types are reported, from complex partial to primary generalized. Treatment for epilepsy is based on the seizure type, age of child and overall clinical picture. There is no single, specific medication that is more effective for children with ASD/epilepsy.

More than 50% of children with ASD have abnormal baseline Electroencephalography (EEGs), many without clinical seizures. These EEG abnormalities may be reflective of the brain dysfunction that is associated with ASD. Current research efforts have focused on more careful characterization of the EEG in children with ASD in order to determine if abnormalities or differences thatmay predict clinical outcomes. At present it is not recommended to treat abnormal EEG patterns in the absence of clinical seizures.

SLEEP IMPAIRMENT

The prevalence of sleep problems in ASD ranges from 53-78%, compared to 26-32% of typically developing children. The primary sleep problem in ASD is insomnia, or the inability to sleep. The key components of pediatric insomnia are difficulty falling asleep and difficulty staying asleep, often related with frequent nighttime awakenings. Children with sleep impairment also have a higher rate of intellectual disability, behavioral disturbances, and epilepsy.

Unfortunately, sleep problems often remain undetected and untreated, mainly because screening questions are not asked by health care providers. The Sleep Committee of the Autism Treatment Network developed a practice guideline for screening and treating insomnia in children with ASD. The parameters include the following:

1. All children should be screened with the following questions:
    - Does the child fall asleep within 20 minutes?
    - Does the child fall asleep in the parents' bed?
    - Does the child sleep too little?
    - Does the child awaken at least once during the night?
2. Screening for medical reasons for insomnia, such as reflux, constipation, breathing problems, pain, or seizures must be performed.
3. If insomnia is present, initiate the Sleep Education Toolkit (on Autism Speaks website)
4. If insomnia does not resolve over time, consider sleep medications or referral to a specialist.

There are several medication options for insomnia. Melatonin is the most widely studied and used medication.Most practitioners recommend beginning with 3 mg of melatonin to be given one hour before bedtime. Melatonin is most effective for helping the child get to sleep (sleep

onset) and less effective for keeping a child asleep throughout the night (sleep duration). Other medications studied for sleep impairment in ASD include:

- clonidine
- Risperidone
- mirtazapine
- niaprazine
- secretin

GASTROINTESTINAL (GI) DISORDERS

The prevalence of GI disorders is estimated as high as 70%, with symptoms including abdominal pain or discomfort, constipation, diarrhea, or reflux. In 2010, guidelines for the evaluation and treatment of common GI problems in ASD were published in the journal Pediatrics. Specific and detailed guidelines for the evaluation and treatment of (1) constipation, (2) excessive diarrhea, and (3) gastroesophageal reflux disease were provided.

The diagnostic evaluation begins with a thorough medical examination, which can be challenging in these patients. Of note, pain and discomfort can present in unusual ways, such as irritability, self-injury, or sleep disturbance. Therefore, GI problems should always be considered in children with ASD. Many of the standard tests performed in typical children, such as pH probes for reflux, are very difficult to administer in young or developmentally disabled children. As a result, the clinician must rely on the history and examination to make a diagnosis and treat properly.

METABOLIC DISORDERS

Metabolic disorders are rare in individuals with ASD,affecting about 1% of children. Several metabolic disorders are associated with ASD, such as:

- phenylketonuria
- creatine deficiency syndromes
- urea cycle disorders
- Wilson's disease
- Lesch-Nyhan syndrome

Recently there has been growing interest in mitochondrial dysfunction in ASD. Mitochondria provide much of the energy to a cell. Therefore, disorders of the mitochondria more severely affect organs with high-energy demands, such as the brain, heart, and muscles. As a result, children with mitochondrial disease have certain clinical features, such as heart disease, delayed motor development, and cognitive delay. Only in the presence of these features should testing for mitochondrial disorders be performed.

LABORATORY INVESTIGATIONS

In 1999, the Child Neurology Society and American Academy of Neurology formulated Practice Parameters for the Diagnosis and Evaluation of Autism. These formal guidelines have not been revised since (see Figure 2). However, in 2008 and then 2013, revised guidelines for the genetic testing of children with ASD were published. The recommendations provided here are based on the 1999 clinical guidelines and 2013 genetic testing guidelines.

- The only laboratory or imaging study that is recommended for

all children with ASD is genetic testing. All children being tested should undergo a chromosomal microarray analysis. Details about genetic testing are provided in Figure 3.

- An EEG should be performed only if a child has clinical events suggesting seizures or a history of a language regression.
- A brain MRI should only be performed if a child has an abnormal neurologic examination that would warrant neuroimaging or if the child has a genetic mutation that is associated with brain abnormalities.
- Metabolic or mitochondrial testing is only warranted if the child has features that are specific to certain disorders(see Schaefer, 2013 for details).

Figure 2

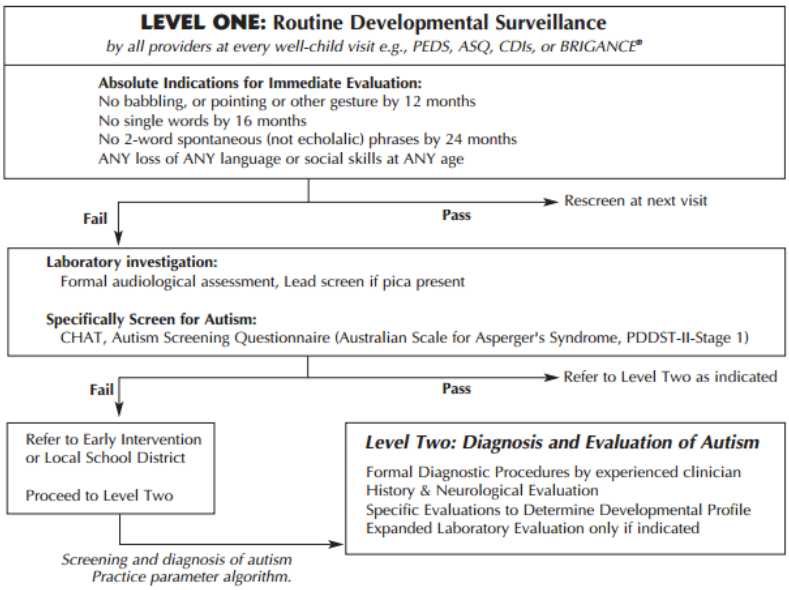

Figure 3

Recommended testing for all children with an ASD diagnosis:

1. Three generation family history
2. Detailed examination to identify known syndromes
3. Chromosomal Microarray
   oligonucleotide array-comparative hybridization OR single-nucleotide polymorphism microarray
4. In some centers exome sequencing is available. Eventually will likely replace CMA

Phenotype Specific Testing:

Males:

1. DNA testing for Fragile X
2. MECP2 sequencing if clinical features are concerning (drooling, recurrent respiratory infections, hypotonia in facial muscles)

Females:

1. MECP2 sequencing
2. DNA testing for Fragile X only if consistent phenotype, + family history for X linked neurodevelopmental disorders, or family history concerning for Fragile X associated tremor/ataxia syndrome
3. **Macrocephaly** (HC > 2.5 standard deviations above mean, or above 98%):
   1. PTEN gene sequencing analysis

Genetic counseling for all children with an ASD diagnosis:

Negative test (no etiology identified):

1. Counseling about recurrence risk based on sibling studies (up to 20% rate)

Positive test (etiology identified):

1. Counseling about specific mutation and associated clinical features (if known), including comorbidities, treatments, prognosis
2. Referral to appropriate specialists

DIAGNOSTIC STANDARDS

DIAGNOSTIC SCREENING

Early screening is critical for the initiation of early interventions that may improve developmental outcomes in children at risk for ASD. Now, a standard screening for ASD is performed by pediatricians at the 18 month visit using questionnaires such as the Modified Checklist for Autism in Toddlers (M-CHAT). If there are red flags for ASD, then the child is referred to a specialist (developmental pediatrician or neurologist), as well as to early intervention services.

DSM

The diagnosis of ASD is based on two factors:

1. the observation of the patient by a trained clinician
2. a detailed history about development and behavior provided by the caregiver and/or patient (depending on age)

The clinical standard of diagnosis is DSM-5, which was reviewed in an earlier section. The change in criteria from DSM-IV TR (earlier version) should be noted here in order to clarify some terms that are still often used. In DSM-IV,patients could be diagnosed with four separate disorders, all of which fell under the umbrella of Pervasive Developmental Disorders (PDD). The deficits seen in PDD fell into three domains:

1. social interaction
2. communication
3. repetitive behaviors/restricted interests

Additionally, there needed to be evidence of impairment by age 3, and this impairment could not be accounted for by Rett syndrome or childhood disintegrative disorder.Specific diagnostic categories included:

1. Autistic disorder: Children with impairment in all three domains (social interaction, communication, repetitive behaviors/restricted interests).
2. Asperger syndrome: Children with impairment in social interaction, as well as the presence of restricted interests/repetitive behaviors, but no deficit in communication, and no history of language delay.
3. Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS): Children with deficits in social interaction and either impairment in communication skills or with the presence of repetitive behaviors/restricted interests. Some considered this a milder form of autism.

In DSM-5 the labels of Asperger and PDD-NOS have been removed and the social and communication categories have been combined into one. All disorders fall under the umbrella of “autism spectrum disorder” with qualifications for severity of symptoms in each domain. These changes allow clinicians to account for the variations in symptoms and behaviors between individuals and to appreciate the true variability of the disorder without having to place individuals in specific categories. Also, the removal of the strict age cutoff of 3 years allows for earlier diagnosis and recognized that in some people symptoms may not emerge until later in childhood

Many large studies that have been performed since the publication of DSM-5 have found that most children who met criteria for PDD in DSM-IV now meet criteria for ASD in DSM-5.

OTHER DIAGNOSTIC TOOLS

Other well-validated tools to diagnose ASD include the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). These tools require standardized clinical training and establishment of reliability with the assessment and scoring. The ADOS takes anywhere from 30 minutes to 1 hour. The ADI takes 2-4 hours to give. It is useful to have a multidisciplinary approach to the evaluation of a child with ASD. This is important because behavior can be variable with different examiners and in different situations. The team should include a child psychologist, psychiatrist, speech and language therapist and an educational consultant.

THERAPEUTIC INTERVENTION

Behavioral interventions are still the maintstay of treatment for improving the core deficits in ASD. The current clinical guidelines from treatment come from a publication entitled “Educating Children with Autism” by the National Research Council (2000), with the following set of recommendations:

1. High treatment intensity (at least 25 hours/week of intervention)
2. High staff: student ratio (at least 1:2)
3. Teachers with special expertise in ASD
4. Individualized program for each child

Most of the intervention programs used for ASD come from a field known as Applied Behavior Analysis, or ABA, which centers on the analysis of the way one’s environment influences behavior. ABA treatment models were first formally studied in the 1960’s by Ivar Lovaas and colleagues. They designed very structured learning settings to target maladaptive behaviors in children with ASD. These interventions led not only to an improvement in these behaviors but also gains in language, social interaction, and adaptive function. Since then, many types of ABA interventions have been designed for children with ASD, and they are briefly summarized below.

Discrete Trial Training (DTT): This approach involves breaking down complex skills into simpler skills that are taught through repeated, structured trials. Instead of teaching an entire skill at once, the skill is broken down and “built-up” using discrete trials that teach each step one at a time. Each trial has a structured set of steps that are clearly defined and scripted and always need to be followed. Each trial requires a response from the child, and with repetition the skill is learned. DTT can be very effective in teaching skills and behaviors to children with ASD. However, because it is very adult directed and scripted, it does not allow for much spontaneous use of skills. Some argue that the skills learned are not always generalized to other environments (such as school or home). In that setting, other forms of intervention have been developed that are more child-directed and naturalistic.

Pivotal Response Training (PRT): This treatment is more play-based and child-directed. Rather than targeting individual behaviors, the PRT therapist targets “pivotal” areas of a child’s development, including responsiveness to multiple cues, motivation, self-management and child self-initiations. The idea is that targeting these key areas will result in improvements in broader areas of social communication and adaptive skills. PRT is loosely structured and relies on naturally occurring teaching opportunities. For instance, if a child is very attached to a particular doll, that doll will be used as a motivation to teach other tasks.

Floortime therapy: This treatment was created by child psychiatrist Stanley Greenspan, M.D. It is based on the premise that adults can help children by working with them at their developmental level and building on their strengths.In floortime, the therapists and parents play with the child through activities that the child enjoys. They follow the child’s lead and build on that play. Therapists teach parents how to direct their children into more complex interactions.
Denver model and Early Start Denver Model (ESDM): This treatment involves an individually tailored program that is developmentally appropriate for the child. Teaching occurs in the child’s natural environment, such as family routines (meals, bathtime, play dates), with focus on the child’s

language and social-emotional development. The ESDM targets toddlers as young as 18 months of age. A large clinical trial showed improvements in overall developmental level, particularly in language, two years after starting treatment.

JASPER (Joint attention symbolic play engagement regulation): This is a play-based intervention that targets joint attention and play skills. It has been shown in several studies to improve social communication (particularly language) in children with ASD. The distinguishing feature of JASPER is the focus on initiation of and response to joint attention and different levels of play. A current study has modified JASPER to treat infants showing red flags for ASD as early as 12 months of age. The JASPER intervention has also been effective in improving communication in minimally verbal children with ASD.

MEDICATIONS

Two medications are approved by the Food and Drug Administration (FDA) for the indication of irritability in children 6 and up with ASD:

1. Risperidone(Risperdal)
2. Arapiprazole (Abilify)

Both medications belong to a class of drugs known as atypical antipsychotics. They target the dopamine and serotonin neurotransmitters in the brain. These medications can be very effective, in combination with behavioral intervention, to improve aggression, self-injury, repetitive behaviors and sometimes overall attention and engagement.While they are not designed to improve the core deficits in autism, these medications work to improve maladaptive behaviors which, in turn, helps children attend more to their school and home environments and, as a result, can improve areas of cognition, language and social interaction. For instance, if a child's self-injury or aggression on the playground improves with risperidone, he will be able to spend more time interacting and engaging with his peers.

The major side effects of these medications are increased appetite, weight gain, and sleepiness.

Additionally, risperidone can increase the body's production of the hormone prolactin, which can interfere with bone building and cause breast swelling in both boys and girls. Usually prolactin levels return to normal after a year of treatment, and levels decrease again after the medication is stopped.

Aripiprazole does not cause a rise in prolactin. If increased too rapidly, it can cause a side effect called "akathisia," which is an intense feeling of restlessness that improveswhen the dose is lowered. Some others may experience abnormal, involuntary, movements, known as dyskinesia, most commonly in the face and mouth.

In our discussion of treatment options it must be emphasized that ASD is a lifelong disability, with the needs of the child changing with different developmental stages. No single treatment offers a cure for ASD. However, these treatments, particularly in combination, can greatly improve a child's function.

Due to the variability in ASD, it is necessary to tailor treatments to the wide

range of symptoms that a child may display. Currently, research is focused on designing and implementing more targeted interventions that are specific to the needs and clinical profiles of each individual child. Research is also using behavioral and brain based markers to define predictors of outcome with specific treatments. Ultimately, the goal in the treatment of children with ASD is to move from a “one size fits all” to a more personalized, individualized approach.

GLOSSARY

Applied Behavior Analysis (ABA): The use of techniques of behavior analysis to increase useful behaviors and reduce those that cause harm or interfere with learning. ABA is used to bring about positive change in behavior in children with a variety of disabilities, including ASD.

Arapiprazole: An antipsychotic medication that works as a partial dopamine agonist in the brain. It is primarily used in the treatment of schizophrenia and bipolar disorder; it is now also FDA approved for treatment of irritability in children with ASD ages 6 and up.

Autism Diagnostic Interview (ADI): A structured interview conducted with the parents of individuals being evaluated for ASD. The interview is used by trained researchers and clinicians for diagnostic purposes in children with mental age of at least 18 months.

Autism Diagnostic Observation Schedule (ADOS): A standardized, play based measure that is performed by a trained researcher or clinician and is considered one of the gold standard tools to diagnose ASD. It is often used in conjunction with DSM-5. There are different modules of the ADOS based on the child’s language ability and it can be performed in children with mental age of at least 18 months.

Autism Spectrum Disorder (ASD): A group of complex disorders of brain development, defined by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors.

Diagnostic Statistics Manual, 5th edition (DSM-5): The 2013 update to the American Psychiatric Association’s classification and diagnostic tool. It is used as the clinical gold standard for psychiatric diagnoses.

Electroencephalography (EEG): A non-invasive test that measures and records the electrical activity of the brain. It is used to diagnose seizures, sleep problems, and sometimes other neurologic disorders.

Epilepsy: A clinical term for a variety of neurological disorders characterized by recurrent seizures.

Insomnia: A sleep disorder characterized by an inability to obtain sufficient sleep for a variety of possible reasons.

Intellectual disability (previously called mental retardation): A term used when a person has limitations in mental functioning and in skills such as self-care. These limitations cause a child to learn and develop more slowly than a typical child. Intellectual disability is measured by IQ tests. When tests have an average score of 100, a child with a score of 70 or less has intellectual disability.

Magnetic resonance imaging (MRI): A non-invasive test that uses a magnetic field to created detailed pictures of the organs in your body and is used to

study the brain. Unlike EEG, which gives you a real-time recording of brain activity, MRI gives a detailed picture of your brain.

Pervasive Developmental Disorder (PDD): A diagnosis that was used in the prior version of DSM (DSM-IV TR), it referred to a group of four disorders characterized by delays in the development of socialization and communication. The four disorders under the PDD umbrella included: Autistic disorder, Asperger syndrome, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder-Not otherwise specified. PDD is not a diagnosis in the new DSM-5.

Risperidone: An antipsychotic medication working on both dopamine and serotonin receptors in the brain. It was first developed to treat schizophrenia; it is now also FDA approved for treating irritability in children with ASD ages 6 and up.

Tuberous Sclerosis Complex (TSC): A genetic disorder that causes non-cancerous tumors in many different organs, including the heart, kidneys, eye, lungs, and brain. Children with TSC are at high risk for ASD and cognitive impairment, as well as epilepsy.

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Figure 2, Practice parameter: Screening and diagnosis of autism: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. Filipek, P; Accardo, P; Ashwal, S; Baranek, G; PhD, OTR; Cook, E; Dawson, G; Gordon, B; MD, PhD; Gravel, J; Johnson, C; MEd, MD; Kallen, R; Levy, S; Minshew, N; Ozonoff, S; Prizant, B; PhD, CCC-SLP; Rapin, I; Rogers, S; Stone, W; Teplin, S; Tuchman, R; Volkmar, F Neurology. 55(4):468-479, August 22, 2000.