

UPDATE ARTICLE

Autism spectrum disorders: an overview on diagnosis and treatment

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Pervasive developmental disorders are now commonly referred to as autism spectrum disorders (ASDs). ASDs present with a range of severity and impairments, and often are a cause of severe disability, representing a major public health concern. The diagnostic criteria require delays or abnormal functioning in social interaction, language, and/or imaginative play within the first 3 years of life, resulting in a deviation from the developmental pattern expected for the age. Because establishing a diagnosis of ASD is possible as early as 18-24 months of age, clinicians should strive to identify and begin intervention in children with ASD as soon as signs are manifest. Increasing efforts are underway to make ASD screening universal in pediatric healthcare. Given the crucial importance of early identification and multiple modalities of treatment for ASD, this review will summarize the diagnostic criteria, key areas for assessment by clinicians, specific scales and instruments for assessment, and discussion of evidence-based treatment programs and the role of specific drug therapies for symptom management.

Keywords: Autistic disorder; pervasive development disorders; diagnosis, treatment

Introduction

According to the American Psychiatric Association's DSM-IV,¹ the category of pervasive developmental disorders (PDDs) includes autistic disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), childhood disintegrative disorder (CDD, Heller's syndrome), and Rett's disorder. This group of disorders is characterized by a shared spectrum of qualitative impairments in social interaction, associated with varying degrees of deficits in communication and marked repetitive behaviors and restricted interests. PDDs are now commonly referred to as autism spectrum disorders (ASDs). Diagnosing ASD requires a comprehensive, systematic, and structured approach. Besides meeting the goal of identifying the disorder, the diagnostic assessment provides important information on the child's relative strengths and weaknesses, identifies which maladaptive behavior and comorbid difficulties are present, clarifies the impact of the child's condition on the family, and benchmarks the developmental skills of the patient. In this way, the assessment should establish a roadmap for treatment by identifying the capabilities and challenges for the child and providing useful information

on the needs and skills that must be addressed by intervention. Because establishing a reliable diagnosis of ASD is possible as early as 18-24 months of age, clinicians should strive to identify and begin intervention in children with ASD as soon as signs are manifest.²

Epidemiology

The pioneering epidemiologic study in autism was conducted by Victor Lotter in the 1960s in England.³ Studies conducted after the 1990s detected estimates of autistic disorder prevalence between 10 and 16 per 10,000 inhabitants, while the current estimated rates of PDD are approximately 60/10,000,^{4,5} representing a nearly 10-fold increase compared to earlier reports in the literature. Epidemiologic surveys from around the world have found individuals with ASD in all studied regions, and with roughly similar prevalence rates.⁶ PDD-NOS is routinely found to be the most frequent diagnosis (3/1,000), followed by autistic disorder (2/1,000), while Asperger's disorder is significantly less common (6/10,000). Rett's disorder and CDD are very rare (2/100,000).⁷ A recent study by the U.S. Centers for Disease Control Prevention (CDC), using a surveillance system, found an overall prevalence of approximately 1% for ASD in several regions of the United States.⁸

Only four studies presenting epidemiological data from Latin American countries have been published.⁶ In Brazil,

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a pilot study of the prevalence of ASD was conducted at a local administrative area in the state of São Paulo. The study included 1,470 children aged 7 to 12 years old and was based on a combination of standardized instruments and clinical assessments using the DSM-IV criteria. The survey estimated a prevalence of ASD of 0.3%, and some hypotheses were raised to explain this low frequency, the main one being the small sample size.⁹ Taken together, the combined prevalence of ASDs makes them one of the most frequent neurodevelopmental disorders, representing a major public health concern.

Diagnostic criteria

The current specific criteria for ASD diagnoses are drawn from three domains:

- i) Impaired social interaction, as shown by: a) marked impairment in the use of non-verbal communicative behaviors (such as eye-to-eye gaze, facial expression, body postures); b) failure to develop age-appropriate peer relationships; c) a lack of spontaneous sharing of affect and interests with others; and d) lack of social or emotional reciprocity (limited interest in or awareness of others' reactions, interests, or feelings).
- ii) Qualitative impairments in communication skills, as shown by: a) delays in, or lack of, language acquisition (absence or reduced frequency of early language development as babbling and playing with sounds, and later, absence of phrase speech); b) inability to initiate or maintain a conversation; c) stereotyped and repetitive use of language or idiosyncratic language (echolalia, oddly formal speech, neologisms); and d) lack of development of age appropriate pretend play or social imitative play.
- iii) Presence of restricted and repetitive patterns of behavior, interests and activities, as shown by: a) pronounced preoccupation with one or more unusual and restricted interests; b) inflexible adherence to specific routines or rituals; c) motor stereotypies (hand flapping, finger flicking, pacing, and jumping); and d) preoccupations with parts of objects.

In order to meet full criteria for autistic disorder, the individual must have evidence of a total of six or more items from domains i), ii), and iii), with at least two items from i), and one each from ii) and iii). Individuals with Asperger's disorder by definition are considered to have no clinically significant language delays, and must manifest two or more criteria from i) and at least one criterion from repetitive, restricted interests (iii). The diagnosis of PDD-NOS is considered a form of sub-threshold autism or autism with atypical features in individuals with severe and pervasive social communication impairments and/or impairing restricted interests and repetitive behaviors, but where the required criteria for autistic disorder or Asperger's disorder is not met. Rett's disorder and CDD have distinct developmental and behavioral profiles (severe deceleration of motor skills and head growth between 5 to 30 months for Rett's disorder and marked, pervasive developmental

and behavioral deterioration after apparently normal development for at least 2 years in CDD).

The diagnostic criteria require the appreciation of delays or abnormal functioning in social interaction, language, and/or imaginative play within the first 3 years of life, resulting in a deviation from the developmental pattern expected for their age.¹⁰ Hence, a priority is to identify early signs of ASD and initiate interventions as soon as possible, as it is widely recognized that early intervention results in a better prognosis.¹¹ Longitudinal studies of infants at high-risk for autism by virtue of having an older affected sibling, and retrospective examinations of first-birthday videos in children later diagnosed with autism confirm that, in some children, the delays and deviations of ASD are identifiable between 6 and 12 months of age,¹² becoming more stable after 18 months of age.¹³ Autism diagnoses at 24 months of age have been found to be stable over follow-up periods of several years. Although the first symptoms described in the literature are related to social communication, these longitudinal studies have shown that infants with other more non-specific signs not related to sociability can be identified even earlier. These signs include irritability, lack or excess of responsiveness, changes in activity level, and deficits in gross motor development.¹⁴ Retrospective reports from the CDC autism surveillance network noted that more than 50% of parents of children with autism had voiced concerns about their child's development or behavior in the first 12 months of life, and that 80% had identified concerns about language development by 36 months.¹⁵ Clinicians are strongly encouraged to take note of such early concerns and possible deviations and consider intervention, rather than to suggest prolonged monitoring.

The DSM-5 has just been officially released and in its most recent text renames the category as ASD, with significant changes in the diagnostic classification and criteria for the PDDs as compared to the DSM-IV according to a recent editorial on the subject.¹⁶ The main changes in the diagnosis criteria are presented in Table 1.

Screening evaluations

In the United States, pediatricians are recommended to perform routine specific ASD screening at 18 and again at 24 months.¹⁷ The approach to screening assessments for suspected ASD includes the following:

ASD specific symptom screening for DSM criteria in primary care or general medical settings (Level 1). These screening approaches can be performed using completion of well validated checklists, such as the Developmental Behavioral Checklist-Parent (DBC-P),¹⁸ the Modified Children's Autism Test (M-CHAT),¹⁹ the Autism Behavior Checklist (ABC),²⁰ or the Autism Screening Questionnaire (ASQ).²¹ For those children identified as high-risk for ASD by virtue of positive initial screening, more in-depth assessments should then be pursued (Level 2). These include:

Table 1 Changes in the diagnostic criteria for the PDDs in the DSM-5 (adapted from Ozonoff¹⁶)

- 1) The category of pervasive developmental disorders will be replaced with ASD.
- 2) Three symptom domains will be collapsed into two domains: social communication (comprising elements of impaired social interaction and impaired communication), and restricted interests and repetitive behaviors.
- 3) Creation of a single diagnosis (ASD) with the elimination of Asperger's disorder.
- 4) Rett's disorder will be eliminated.
- 5) Number of symptoms condensed from 12 to seven merging criteria that were overlapping and eliminating symptoms that are not specific to ASD (e.g., delayed development of language).
- 6) Inclusion of a new symptom of unusual sensory sensitivity within the restricted interests and repetitive behaviors domain.
- 7) Addition of a severity criterion that will clarify the nature of the spectrum, as well as its variability, such as intensity and duration of symptoms, amount of impairment associated.
- 8) Establishment of a new social communication disorder category to provide diagnostic coverage to individuals who only have social communication problems but do not display the repetitive and stereotyped behaviors of ASD.

ASD = autism spectrum disorder; PDD = pervasive developmental disorder.

- 1) The Childhood Autism Rating Scale (CARS).²²
- 2) Determination of social abilities and adaptive skills. The Social Responsiveness Scale (SRS),²³ completed by a parent, can provide information relating to social abilities. The Vineland Adaptive Behavior Scales (Vineland-II, 2nd edition)²⁴ can be administered by a clinician or completed by parents to assess adaptive skills.
- 3) Screening for maladaptive behaviors and comorbid problems (e.g., hyperactivity, irritability, aggression, temper outbursts, self-injury, mood, anxiety symptoms) can be assessed by means of parent or caregiver completion of the Aberrant Behavior Checklist-Community Version (ABC-CV).²⁵
- 4) Screening for medical comorbidities (history of elimination disorders, seizures, gastrointestinal problems, growth abnormalities). The role of medical testing in the assessment of ASD is increasing, although full consensus is lacking as to what tests are considered universally appropriate. Examples include possible electroencephalogram testing, given that the rate of comorbid epilepsy in ASD varies between 15-30%. When epilepsy is present, a neurologist assessment should be indicated.
- 5) Screening for indicators of genetic syndromes associated with autism (family history, dysmorphic features, head size, café au lait spots, inherited metabolic disorders). Currently, it is recommended that if the patient presents with mental retardation, minor physical anomalies, syndromic features or family history, genetic evaluation should be suggested. The indications for molecular genetic testing are rapidly expanding, with many specialists now recommending comparative genomic hybridization testing or whole-exome sequencing for individuals with a confirmed diagnosis of ASD.²⁶

Diagnostic instruments

The accepted gold standard diagnostic assessments for an ASD diagnosis are the Autism Diagnostic Observation Schedule (ADOS)²⁷ and the Autism Diagnostic Interview, Revised (ADI-R)²⁸ because of their extensive detail of behavioral and developmental characterization, and their reliability among raters trained in their administration. The original ADI was established for research and was used

to evaluate the behavior of individuals older than 5 years, whose chronological and mental age was at least 2 years, based on diagnostic criteria proposed by the ICD-10 and DSM-IV. Subsequently, the ADI-R was revised and modified to be appropriate for children from mental ages 18 months through adulthood.

The ADOS is a semi-structured clinician-administered interview that assesses a wide range of ASD-specific characteristics including verbal and non-verbal communication, reciprocal interaction, and conversational ability. It requires approximately 45 minutes for administration. There are separate ADOS modules based on age, language, and developmental level, such as the ADOS-T for toddlers, and Modules 1-4 that are validated for children, adolescents, and adults. It is important to note that both ADI-R and ADOS need specialized training for administration, but they can be administered by a wide range of specialists. The ADI-R has already been translated and validated in Brazil²⁹ and there is a Brazilian version of ADOS (personal communication by Maria Clara Pacifico, Cristiane S de Paula, and Guiomar Oliveira, 2012).

Complementary evaluations

Assessment of developmental level of intellectual abilities

Cognitive dysfunction is nearly ubiquitous in ASD and important in determining overall functional capacity, although the severity and breadth of cognitive deficits vary widely in individuals on the spectrum.³⁰ Additionally, it is important for the differential diagnosis or co-occurring diagnosis with mental retardation. In cases of patients with autism, approximately 60-70% have some level of intellectual disability (mental retardation), whereas most individuals with Asperger's disorder and PDD-NOS test in the normal range of intelligence, albeit with frequent, more compartmentalized areas of deficits.³¹ Conversely, around 10% of individuals with ASD have remarkable skills for their age ("savants"), often representing highly specialized and restricted skills not in keeping with their impaired global functioning.¹⁰ Even among those ASD individuals deemed to be high-functioning, by virtue of scoring within the normal range of full scale IQ measures, neuropsychological testing routinely reveals cognitive dysfunction, particularly on executive functions and social

cognition, such as set-shifting, planning, inhibitory control, and theory of mind deficits.³²

Assessment of developmental level of language

A speech therapist evaluation is important since approximately 20-30% of ASD individuals are nonverbal and between 20 and 25% of them present a developmental history of marked regression in terms of loss of previously acquired language.³³ Some pre-verbal skills, such as joint attention, response to speech, gestures, imitation, and symbolic play, are considered strong predictors for early verbal communication.^{34,35} Identifying impairments of these skills is important for intervention as these represent foundational skills for language acquisition. Delays are also seen in the transition from the use of isolated to combined words. A study from Paul et al.³⁶ showed that even children with ASD who have achieved productive use of isolated words and have a repertoire in their expressive vocabulary of 100 words at 28 months are still at high risk to not progress to sentence production with more than one word. In contrast, 28-month-old children with typical development and who have the same size of vocabulary repertoire are uniformly able to combine words into phrases. Although many children with ASD present significant progress in language in the period from 24 to 48 months, with vocabulary expansion and scores within the mental age showed by appropriate tests of receptive and expressive abilities, their overall communication ability remains impaired. While the lack of acquisition of phrase speech by age 5 years has often been cited as predicting severely limited lifetime language development, recently descriptions of later emergence of language have been described in a number of cases.³⁷ When children with ASD begin to talk, some distinctive features in the language form and content appear, such as echolalia. Echolalia is the repetition of other's speech and it can be immediate or delayed, partial or total. Echolalia was initially seen as an undesirable and

dysfunctional behavior, however, current studies³⁸ suggest children use it as a strategy to communicate. As language skills improve, echolalia tends to disappear.³⁸ The pronoun inversion is another common behavior in the speech of children with ASD and seems to be related to the nature of deictic pronouns, which can be confusing for younger children of the spectrum. In deictic pairs like I/you, the reference changes depending on the viewpoint of the speaker. Children with ASD have particular difficulty with this concept due to the literalness of language and lack of flexibility.³⁹ Even when the subject produces words and grammatically correct sentences, their speech reflects fundamental flaws of understanding and expression of attitudes and intentions. In general, children with ASD have vocabulary with little information. Many start talking only naming specific objects or figures.⁴⁰

Several authors have attempted to define specific profiles of the nature of language impairments in individuals with autism, Asperger's disorder, semantic-pragmatic syndrome, and specific language impairment.⁴¹⁻⁴⁵ However, because many characteristics are found to be overlapping and/or are interrelated, such differences are often found to be subtle and highly individualized making a speech evaluation necessary. In Table 2, characteristics of each disorders are summarized. To sum up, it can be concluded that children with ASD have more difficulties in linguistic structure, interests, and social use of language. Individuals with Asperger's syndrome by definition display fewer problems with linguistic structure, but do manifest pragmatic difficulties, and deficits in the effective social use of language. Children with semantic-pragmatic disorder, in contrast, have difficulties in understanding linguistic structures and social interest.⁴⁶⁻⁴⁸

Treatment

Over the past two decades, with the increased number of infants and toddlers diagnosed with ASD, there is a need for effective and appropriate interventions for the children

Table 2 Differential diagnosis of language disorders

Autism	<ul style="list-style-type: none"> - Atypical verbal language, such as failures in the use of gestures, facial expressions, and gaze exchange - No verbalization or atypical forms, content and use of language (echolalia, pronoun reversal) - Impairment in receptive language - Commitment in symbolic play - Restricted interests
Asperger's syndrome	<ul style="list-style-type: none"> - Absence of delayed speech - Absence of cognitive impairment - Ability to memorize large amounts of information - Restricted interests - Impairment in reciprocal social interaction
Specific language impairment	<ul style="list-style-type: none"> - Delay in language development not overcome until 5 years old - Difficulty with the structural aspects of language - High occurrence of deviant phonological processes (not observed in the normal process of language acquisition) - Overuse of gestures and vocalizations - Short speeches, often with inadequate cohesion and coherence
Pragmatic language impairment	<ul style="list-style-type: none"> - Inability in understanding and maintaining conversation - Failures of content and form in sentence construction - Inappropriate social responses - Tangential speech

and their families that address core impairments and co-occurring conditions.⁴⁹ The National Research Council (NRC)⁵⁰ conducted a systematic review of research on interventions for children with ASD from birth through 8 years of age. Few well-controlled studies were conducted to test the effectiveness of specific modalities of intervention. Priority for instruction should be in a) functional, spontaneous communication, b) social instruction across settings, c) play skills, with a focus on peer interaction, d) new skill maintenance and generalization in natural contexts, and e) functional assessment and positive behavior support to address problem behaviors. Intervention effects should be evaluated regularly at 3-6 months intervals, focusing on: a) social skills, b) communication skills, c) adaptive skills, d) organizational skills. Table 3 shows the essential characteristics of effective interventions for children with ASD determined by the NRC. Lack of significant progress in any domain over a 3-6 month period should prompt modification of treatment approach or intensity.

Treatment approaches

Parent training

Parental and family involvement is considered an essential element of intervention programs for children with autism.⁵⁰ The basic assumption of behavioral parent training is that child behavior is learned and maintained through contingencies within the family context and that parents can be taught to change these contingencies in order to promote and reinforce appropriate behavior.⁵¹

Evidence involving young children supports the recommendation of parent training as an effective method for increasing social skills. However, the manner in which parents are incorporated into the intervention process is important, as well as individualizing the parent education program to consider different family needs and circumstances; not every parent benefits from traditional behavioral parent education programs. Parent education appears to work best with highly motivated and well-functioning adults who are not coping with additional psychological or life stressors, which interferes with their acquisition and implementation of positive parenting strategies.⁵² The literature documents the effectiveness of parent education programs and the lack of maintenance of behavioral gains when parents do not participate in their children's interventions programs.⁵³⁻⁵⁵

Applied behavioral analysis

Applied behavior analysis (ABA) is the science of behavior modification in which procedures derived from

the principles of operant learning are applied to improve socially adaptive behavior and acquisition of new skills through intensive practice and targeted reinforcement.⁵⁶ ABA utilizes a process that begins with the development of treatment plans outlining the purpose and function of behavioral excesses or deficits, selection of appropriate techniques, and continual evaluation and modification of the treatment through systematic data collection. Functional behavioral assessments are a related set of assessment strategies that provide information on the variables associated with a specific behavior.⁵⁷ The operant learning techniques used in ABA intervention for ASDs children are:

- Positive reinforcement: use of praise, snack, food, toys to increase desired behaviors;
- Shaping: rewarding approximations or components of a desired behavior until target behavior is exhibited;
- Fading: reducing prompts to increase independence;
- Extinction: removal of reinforcement maintaining a problem behavior;
- Punishment: applying undesired stimulus to reduce problem behaviors;
- Differential reinforcement: reinforcing a socially acceptable alternate or absence of a behavior.

Intervention programs based on ABA are currently viewed as the first-line treatment for ASD in early childhood.⁵⁸ Both the UCLA/Lovaas model and the Early Start Denver Model (ESDM), which are comprehensive early intervention programs built on a framework of ABA, have high quality research reports documenting their efficacy,⁵⁹ especially for improving cognitive performance, language skills, and adaptive behavior. However, in the seminal study evaluating the benefits of ESDM, even after 2 years of intensive intervention (more than 20 hours/week), all children in the active treatment group still met criteria for ASD, documenting the challenge of ameliorating social deficits.⁶⁰ The Early Intensive Behavioral Intervention (EIBI) is a behavioral strategy utilized in the Lovaas⁶¹ study and is the ABA model with the strongest empirical support to date.⁵⁷ EIBI utilizes operant learning approaches to reduce problem behaviors and discrete trial training to develop new skills, such as attention, imitation, receptive/expressive speech and life skills. Core features of the EIBI are:

- 1) Focus on early development (children younger than 5 years);
- 2) Intensity (one-on-one and small group instruction, 20-40 hours/week);
- 3) Adult-directed methods;
- 4) Systematic approach (breaking down skills into basic components);

Table 3 Essential characteristics of effective interventions for children with autism spectrum disorder

- 1) Start intervention programs as earlier as possible.
- 2) Intensive treatment, 5 days a week for a minimum of 5 hours per day.
- 3) Use of repeated planned teaching opportunities that are structured over brief periods of time.
- 4) Sufficient individualized adult attention on a daily basis.
- 5) Inclusion of a family component, including parent training.
- 6) Mechanisms for ongoing assessment with corresponding adjustments in programming.

- 5) Comprehensive nature (e.g., the targets include communication, socialization, adaptive behaviors, problem behaviors).

Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH)

TEACCH is a classroom based, clinical service and professional training program, developed at the University of North Carolina, at Chapel Hill, and started in 1972 by Eric Schopler.⁶² This program has been incorporated widely into North American educational settings and has contributed significantly to the evidence base of autism interventions. The TEACCH approach is called structured teaching because it is based on evidence and observation that individuals with autism share a pattern of behaviors, such as the ways individuals think, eat, dress, understand their world, and communicate. The essential mechanisms of structured teaching consist of organizing the environment and activities in ways that can be understood by the individuals; using individuals' relative strengths in visual skills and interest in visual details to supplement relatively weaker skills; using individuals' special interests to engage them in learning; and supporting self-initiated use of meaningful communication.

Cognitive-behavioral therapy (CBT)

A growing number of reports have begun to provide moderate evidence for the efficacy of CBT approaches for school-age and young adolescents with ASD.^{55,63} Improvements in anxiety, self-help, and daily living skills have been reported, with 78% of 7-11 year-olds in the CBT-treated group rated as positive responders in one trial.⁵⁵ Such findings encourage the consideration of modified CBT approaches to address anxiety in high-functioning children with ASD, which is important given that as many as 30-40% of children with ASD report high levels of anxiety-related symptoms.

Pharmacological treatment for target symptoms

Pharmacological treatment in ASD is widely employed as an adjunctive treatment approach in the majority of individuals with ASD across the lifespan.^{64,65} The best-established goals of pharmacotherapy are to control often associated target symptoms, such as insomnia, hyperactivity, impulsiveness, irritability, auto and hetero-aggressiveness, inattention, anxiety, depression, obsessive symptoms, tantrums, anger attempts, repetitive behaviors or rituals. Numerous studies have reported an increased prevalence of psychiatric comorbidities in this population.^{66,67} Simonoff et al. found that 70% of subjects with ASD had at least one comorbid psychiatric disorder and 41% had two or more diseases. Comorbid symptoms often compound the functional impairments in patients with ASD and may limit the effectiveness of non-pharmacological interventions. At present, there are no available drugs to treat the core social and communication

deficits of autism, although this is a subject of intensive research efforts with agents such as arbaclofen, oxytocin, and mGluR5 antagonists as examples of potentially disorder-modifying treatments under study.

Despite varying levels of empirical support for some targeted medication choices, drug treatment of children and adults with ASD is common clinical practice. Around 45-75% of children with ASD are medicated with psychotropic drugs.^{64,65} Most commonly prescribed medicines, in order of frequency, are antidepressants, antipsychotics, anti-convulsants, and stimulants, many of them without definitive studies guiding their usage. It should be noted that most psychotropic use in ASD is off-label, as there are currently just two medications (risperidone and aripiprazole) approved by the Food and Drug Administration (FDA), and only for the treatment of associated behaviors.⁶⁸

Based on parental reports, the most difficult behaviors of children with ASD are low frustration threshold, distractibility, irritability, inattention, hyperactivity, compulsive repetition, isolation, mood instability, and stereotyped hand movements.⁶⁹

Aggressive behavior and irritability

More than 50% of children with autism show self-aggression, and as many as 14.6% practice severely intense self-aggression that may lead to hospitalization, institutionalization, removal from less restrictive school settings, and a worse prognosis.^{70,71} The causes of irritability and aggression are multifactorial: comprehension difficulties, decreased ability to communicate and express their needs and desires, reduced confrontation skills, conflict with colleagues and authority figures, psychosocial dysfunction, undiagnosed pain, mood and anxiety disorders.⁷⁰ The first step to address the aggressive behavior is to identify the cause and then find the most appropriate therapeutic approach (behavioral management and/or medication). First- and second-generation antipsychotics have shown moderate to large benefits in controlling aggressive symptoms in autism.⁷⁰ In 2002, the Research Units in Pediatric Psychopharmacology (RUPP) Autism Network reported on a multicenter clinical trial that evaluated the efficacy of short- and long-term risperidone in children and adolescents aged 5-17 years with autism accompanied by with tantrums, aggression, self-injurious behavior.⁷² The results showed that short-term risperidone treatment was markedly superior to placebo in these cases (positive responders: 75 vs. 12%, respectively), reducing maladaptive behaviors broadly, including decreased irritability (aggression, agitation, severe temper outbursts), decreased hyperactivity, and reductions in stereotypies. Risperidone treatment was well tolerated for up to 6 months; side effects found to be common in earlier studies with haloperidol were comparatively lower with risperidone. Drowsiness and weight gain were the most commonly reported side effects. Most of seven randomized clinical trials with risperidone, two re-analyses and two association studies demonstrated some efficacy regarding analyzed parameters (irritability, aggressiveness, hyperactivity, general functioning)⁷³⁻⁸¹

with risperidone. Effective doses were low, averaging 2 mg per day. There was no evidence of tolerance or need to increase the dose in subjects followed for up to 6 months of treatment. Recently, the FDA approved aripiprazole for treatment of irritability in children with autism aged 6 to 17 years with severe irritability. Two double-blind, placebo-controlled clinical trials showed that aripiprazole is effective in treating irritability, hyperactivity, and stereotypies in ASD.⁸²⁻⁸⁴ In addition, aripiprazole has been reported to be well tolerated in dose ranges of 5-15 mg per day, and is associated with lower mean weight gain compared to many other atypical antipsychotics, as measured during the initial 8 weeks of exposure.

Two randomized clinical trials with few children with ASD using haloperidol showed significant positive effects on behavioral symptoms and global functioning.^{85,86} Using scales of autistic symptoms (ABC), Miral et al.⁸⁷ compared the effects of haloperidol and risperidone treatment with the latter being superior only for the total score. These studies suggest a positive role of haloperidol for the treatment of children with severe or refractory autism.⁷³ However, extrapyramidal side effects are common with haloperidol, increasing concern over possible long-term effects of exposure in this population.

Other atypical antipsychotics need further clinical evaluation. Olanzapine has not been studied in randomized placebo-controlled trials in children or adults with ASD. However, some case studies^{88,89} and an open trial⁹⁰ reported positive results. Additionally, a randomized trial with a parallel control group treated with haloperidol⁹¹ reported positive results, although patients had significant weight gain. The prolonged use of olanzapine may induce significant metabolic changes, which hampers its use in children and adolescents with ASD.⁹² Ziprasidone was studied in one open study (2007) that included 12 adolescents with ASD treated with ziprasidone, with doses ranging from 20 to 160 mg/day. A 75% response rate to treatment was observed according to the parameters of the Clinical Global Impression (CGI). In addition, there was an improvement in the ABC subscales of irritability and hyperactivity. Ziprasidone did not cause weight gain, but a regular increase in the QTc interval of 14.7 milliseconds in the sample was described.⁹³ Another open clinical study⁹⁴ and a retrospective review of clinical records⁹⁵ showed promising results for ziprasidone in patients with ASD. Double blind, placebo-controlled studies are needed to validate the use of ziprasidone in this population. An open trial with a small number of individuals concluded that quetiapine was poorly tolerated and ineffective in ASD.⁹⁶ There is no evidence to substantiate clozapine usage taking into account the presence of potentially serious side effects such as seizures and neutropenia, with only case reports available.⁹⁷

Repetitive behavior

Most studies of selective serotonin reuptake inhibitors (SSRIs) have shown lack of clinically significant efficacy in the treatment of repetitive behaviors and restricted

interests of autistic spectrum patients.^{98,99} Only one methodologically relevant study showed some positive results of a SSRI (fluoxetine) compared to placebo,¹⁰⁰ but improvements were small. In the largest study of the treatment of repetitive behaviors in ASD comparing citalopram to placebo, no benefits were found for citalopram, and side effects, such as hyperactivity, insomnia, and behavioral deterioration, were common.¹⁰¹ Interestingly, in contrast to studies in children, two, rigorous, placebo-controlled studies showed benefits for fluvoxamine and fluoxetine on measures of repetitive behaviors for adults,^{102,103} however again the benefits in the fluoxetine study were small relative to placebo. Taken together, there is limited evidence to support the use of SSRIs as treatment for repetitive behaviors in ASD. No large-scale controlled trials have examined their effects for the treatment of anxiety or depressive symptoms in individuals with ASD.

Hyperactivity, impulsivity, and inattention

Symptoms of attention deficit hyperactivity disorder (ADHD) are very common in individuals with ASD, affecting between 28-74% of children.^{64,104} Short attention span is observed in 50% of children with autism, hyperactivity in 49 and 21% according to parents and teachers, respectively.¹⁰⁵ Children with ASD and ADHD have higher risk of suffering adverse effects from stimulant treatment than typically developing children with ADHD, showing lower rates of positive responders and less symptomatic improvement.¹⁰⁶ To date, only clinical trials have been conducted with methylphenidate and atomoxetine in ASD. Three randomized clinical trials investigated the effects of methylphenidate in children with ASD.¹⁰⁷⁻¹⁰⁹ Three doses of medication compared to placebo were tested in a clinical trial with 66 participants with ASD in a crossover design.¹⁰⁹ This study was classified as showing strong clinical evidence since 49% of subjects were rated to be positive responders by virtue of showing > 25% decrease in ADHD symptoms from baseline and CGI-Improvement rating of much improved or very much improved. However, 18% dropped out of the trial due to inability to tolerate the medication.⁸² Two other small studies with 10 and 13 children have been judged to be solidly designed, leading to the determination of a promising level of evidence for treatment with methylphenidate for hyperactivity in children with ASD.⁸² Doses examined were moderate in the RUPP study, based on 0.125, 0.25, and 0.5 mg/kg per dose, administered three times daily, 0.125-0.5 mg/kg/day or, 0.3-0.6 mg/kg/day. A small, randomized, controlled clinical trial was conducted with atomoxetine, a selective inhibitor of the reuptake of norepinephrine, in 16 children aged 5 to 15 years old with autism and ADHD. The treatment resulted in a response rate of 43% defined as a 25% improvement on the ABC-Hyperactivity subscale and CGI. A significant improvement over placebo in the hyperactivity/impulsivity subscale was also observed.¹¹⁰ Adverse effects were relatively mild.⁷³ A recent European trial found evidence for superiority of atomoxetine vs. placebo on ADHD symptom measures,

but no difference in response rates, which were low (21 vs. 9%, respectively).¹¹¹

Sleep problems

Insomnia and sleep cycle disruptions are common in ASD. Comparing the sleep patterns of 59 children with ASD aged 4 to 10 years old with 40 controls, the authors found a prevalence of 66% for moderate sleep disorders in patients with ASD.¹¹² The literature shows a prevalence rate of sleep disorders ranging from 40 to 86% in ASD.¹¹³ These symptoms produce functional impairment and increased irritability influencing patient outcome and decreasing the family's quality of life. Many medications are used because of their sedative profile to treat sleep disorders: second-generation antipsychotics, antihistamines, benzodiazepines, alpha-agonists; however, none of them has been evaluated by a controlled clinical trial. Supplemental melatonin has shown promise in treating initial insomnia in children with autism, with several studies replicating the improvement in sleep induction.¹¹⁴ In addition, this agent is well tolerated by patients. A meta-analysis conducted in 2011 found 18 papers, of which five were randomized placebo controlled clinical trials that evaluated the use of 1 to 6 mg/day of melatonin to treat sleep disorders in patients with ASD. All of them reported significant improvement in total sleep duration, number of awakenings, and reduced latency to sleep onset.¹¹³

Seizures

Although most children with autism do not have seizures, the risk of having seizures is still much higher than in typical children. Among patients with autism, 20-25% will have seizures. A recent study¹¹⁵ confirmed some previous findings that 22% of participants developed epilepsy. In the majority, seizures began after 10 years of age. Generalized tonic-clonic seizures predominated (88%). In over half (19/33), seizures occurred weekly or less frequently and in the majority of individuals (28/31) and were controlled with the use of one to two anticonvulsants. Epilepsy was associated with gender (female), intellectual disability, and poorer verbal abilities. Although the presence of epilepsy in the probands was not associated with an increased risk of epilepsy in their relatives, it was associated with the presence of a broader autism phenotype in relatives. This indicates that the familial liability to autism may be associated with the risk for epilepsy in the proband. When seizures are present, a neurological assessment is very important. The effective and safe use of many anticonvulsants requires regular needs blood drug level monitoring. It is important to note that valproic acid, the most used drug,¹¹⁶ can take several weeks to exert effects. However, because it may have moderate benefits in irritability and severe tantrum, valproic acid deserves consideration in the context of both symptom targets.¹¹⁷ Topiramate can be used in a range of seizure types and could be tried when either valproic acid or carbamazepine

has failed to stop seizures, or in situations where these medications are contraindicated. Using topiramate could be an important choice given the suggestion that combined use with risperidone may increase benefits in irritability in children with ASD. Topiramate may also have beneficial effects in reducing antipsychotic-induced appetite and weight increases.^{118,119}

Conclusion

ASD represents a major public health concern as a prevalent neurodevelopmental disorder with pronounced risk for failure of adaptation across social, educational, and psychological outcomes. Because the identification of delays and deviations of ASD is possible as early as 18-24 months of age, pediatricians should strive to identify and begin intervention in children with ASD as soon as signs are manifest. Specific scales and instruments should be used to assess clinical manifestations and guide the construction and monitoring of comprehensive treatment programs. True recovery of autism is not reported in the literature, but educational, psychosocial, and language therapies, often combined with adjunctive treatments, such as drug therapy for specific symptoms, are well established for their benefits in ASD. The complex and pervasive nature of ASD requires a team of multiple professionals for accurate diagnosis and clinical care.

Disclosure

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