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Autism spectrum disorder

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Abstract

Autism spectrum disorder is a term used to describe a constellation of early-appearing social communication deficits and repetitive sensory–motor behaviours associated with a strong genetic component as well as other causes. The outlook for many individuals with autism spectrum disorder today is brighter than it was 50 years ago; more people with the condition are able to speak, read, and live in the community rather than in institutions, and some will be largely free from symptoms of the disorder by adulthood. Nevertheless, most individuals will not work full-time or live independently. Genetics and neuroscience have identified intriguing patterns of risk, but without much practical benefit yet. Considerable work is still needed to understand how and when behavioural and medical treatments can be effective, and for which children, including those with substantial comorbidities. It is also important to implement what we already know and develop services for adults with autism spectrum disorder. Clinicians can make a difference by providing timely and individualised help to families navigating referrals and access to community support systems, by providing accurate information despite often unfiltered media input, and by anticipating transitions such as family changes and school entry and leaving.

Introduction

In the past 50 years, autism spectrum disorder (ASD) has gone from a narrowly defined, rare disorder of childhood onset to a well publicised, advocated, and researched lifelong condition, recognised as fairly common and very heterogeneous. The description of the core features of ASD as being social communication deficits and repetitive and unusual sensory–

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Declaration of interests

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motor behaviours has not changed substantially since its original delineation.[1] However, autism is now seen as a spectrum that can range from very mild to severe. Nevertheless, many (but not all) individuals with ASD require lifelong support of some kind.

Although families, teachers, and direct providers make the most differences to the lives of people with ASD, physicians and other clinicians also affect individuals and families by providing information about the current functioning of the person with ASD, by helping caregivers to anticipate transitions, and by navigating referrals to service providers and specialists when needed. ASD represents a substantial economic burden, mainly due to the provision of support to adults who cannot function independently, which results in higher health-care and school costs and loss of income for caregivers.[2] This Seminar focuses on summarising current research so that clinicians can provide guidance to families within the context of ASD, recognising that, although ASD is a biological disorder, it is primarily treated through education and behavioural services, with medication as an important adjunct.

Signs, symptoms, and general diagnostic issues

Although individuals with ASD are very different from one another, the disorder is characterised by core features in two areas—social communication and restricted, repetitive sensory–motor behaviours—irrespective of culture, race, ethnicity, or socioeconomic group.[3] ASD results from early altered brain development and neural reorganisation.[4,5] However, because there are no reliable biomarkers, the diagnosis must be made on the basis of behaviour. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria,[6] published in 2013, were intended to make the diagnosis of ASD more straightforward. There is now a single ASD spectrum based on the two domains (social communication, and restricted, repetitive, or unusual sensory–motor behaviours). Subtypes such as Asperger's disorder and pervasive developmental disorder not otherwise specified, which were unreliably used by clinicians, are now consolidated under the single diagnosis of ASD. In addition, DSM-5 explicitly recognises that ASD can be accompanied by other disorders, including genetic disorders (eg, fragile X syndrome) and psychiatric conditions (eg, attention-deficit hyperactivity disorder [ADHD]).

To be diagnosed with ASD, a person must show evidence of difficulties, past or present, in each of three social communication subdomains, and must have or have had difficulty in two of the four different restricted, repetitive sensory–motor behaviours (panel 1). There are also newly proposed levels of severity in DSM-5 based on the need for support, which so far have shown dubious validity, although the concept of functionality is in itself very important.[7–9]

Questions about screening

Issues related to screening and subsequent diagnosis, both for families and providers, are often different for very young children than for older children, adolescents, and adults, and therefore will be discussed separately. There are no data from well controlled studies about the extent to which early intervention changes adult outcomes, and it is generally not possible to measure the factors that predict later outcomes (eg, language development or

cognitive level) at the ages proposed for early screening (18–30 months). Many public health systems have attempted to identify very young children with ASD in general populations. However, to date, screening methods have typically not been sufficiently sensitive in that they have not identified most children with ASD in general populations in whom parents have not already noticed a delay.[10]

When parents have expressed a concern to a family member, friend, or professional, screening instruments become more predictive for children as young as 18 months of age.[11] Even then, when parents ask for help, referrals are often not made.[12] A range of screening instruments work well when someone—parent or professional—is concerned that a child might have ASD, the most common of which are the Modified Checklist for Autism in Toddlers (M-CHAT) and, less commonly, the Communication and Symbolic Behavior Scales (CSBS).[13] Almost all children identified by these screening instruments have developmental difficulties, although not all have ASD.[13] A survey[14] showed that children with ASD who had consistent sources of paediatric care, frequent contact with grandmothers, and older siblings, received earlier diagnoses than did children with no siblings. Children with ASD who had a younger sibling close in age had the most delayed diagnoses.[15] Thus, many approaches can lead to earlier diagnoses: in addition to screening instruments, strategies include increasing awareness of ASD in the family and community, promoting belief that there is value in getting a diagnosis, facilitating relationships between specialists and primary-care providers to provide screening and make referrals, and improving access to services.

Early diagnosis

ASD can be diagnosed by various professionals (paediatricians, psychiatrists, or psychologists), ideally with input from multiple disciplines. Standardised diagnostic instruments are available, including the Screening Tool for Autism in Toddlers and Young Children (STAT; a 20-min observation for young children) and the more heavily researched Autism Diagnostic Observation Schedule (ADOS;[16] a 45-min observation done by a skilled professional, available in different formats for people of different language levels and ages, from 12 months to adulthood). These instruments allow the clinician, in the company of the caregiver, to observe and characterise the particular behaviours of the individual suspected to have ASD. For research or a more comprehensive developmental history, caregiver interviews such as the Autism Diagnostic Interview-Revised (ADI-R) or, particularly in the UK, the Diagnostic Instrument for Social Communication Disorders (DISCO), or the computer-generated Developmental, Dimensional, and Diagnostic Interview (3di) are used, with many clinicians relying on informal histories.[17,18] Assessment of children's symptoms can be obtained from a variety of scales, such as the Childhood Autism Rating Scale (CARS), Social Responsiveness Scale (SRS), and the Social Communication Questionnaire (SCQ). Adaptive scales are also often used as measures of everyday functioning.[16] Obtaining information about receptive and expressive language level, general behavioural difficulties, and motor skills, including an estimate of cognitive functioning or IQ, is considered standard practice.[19]

Diagnoses based on combined clinician observation and caregiver reports are consistently more reliable than those based on either observation or reports alone; therefore, clinicians should not rely solely on either parent reports or instruments such as the ADOS.[20] Children who do not have language delays, or who are female, of ethnic minorities, of low socioeconomic status, or from families not fluent in English (at least in the USA) often receive later diagnoses.[21]

ASD differs from many other medical conditions in that the family's reactions to the child and the diagnosis affect the child's outcome as much as any specific treatment does.[22] Providing information to family members about resources, even if the next steps are not straightforward, is as important as any diagnostic labels, including ASD and other disorders, that might be applied to the child. Follow-up from a key professional is needed for families, especially at transition points such as diagnosis, school entry and leaving, and family changes. Helping a family to find a child's initial formal treatment is just the first step in what will be many levels of care and many decision points.

Diagnosis, ASD, and intellectual disability

One source of tension regarding the provision of straightforward and simple recommendations for ASD diagnosis and services is the heterogeneity across regions and ages in the association between ASD and intellectual disabilities. Because very young children with clear developmental disabilities are likely to receive referrals for treatment or specialist assessment earlier than those without, care should be taken not to overlook very verbal young children with ASD.[21] Clear predictions of later intellectual disabilities, except in children with profound delays, are not usually possible in children aged 2–3 years referred for possible ASD. Among preschool children in whom ASD is a concern, many but not all (or, in some countries, not most) will have an intellectual disability as well.[23] Statistics vary tremendously, with 11–65% of school-age children with ASD reported as having intellectual disabilities (IQ <70).[24,25] Populations of children in different clinics and research samples can be quite dissimilar, and variation among adults can be even more pronounced, as self-advocates for ASD are often articulate individuals who are in very different circumstances than are people with dual diagnoses of ASD and intellectual disability. Such variation can be confusing for families who do not know what the future will hold for their young children. Therefore, it is important for clinicians and families to know about cognitive and language abilities for children as they grow older and to discuss these issues, as well as to recognise that the relationship between IQ and ASD differs in different populations and at different ages.

Diagnosis in older children and adolescents

For older children (ie, those in later primary school), adolescents, or adults whose families suspect that they might have ASD, questions about diagnosis are different because the individual often already has a history of difficulties.[26] Even though the majority of children with ASD in northern Europe and North America are diagnosed by early school age, there remain others who have never had a diagnosis.[27] Later diagnoses often occur in the context of co-occurring problems such as anxiety, hyperactivity, or mood disorders[22] that might have

either exacerbated or masked the ASD, along with the same factors (female sex, ethnicity, multilingualism, socioeconomic factors, and more advanced language) that play a part in delayed diagnoses in younger children. Assessments of these children need the same ASD-specific clinician observations and caregiver reports as for younger children, with information about speech, language, motor, verbal and non-verbal cognitive, and adaptive skills, but also require attention to relevant psychiatric disorders. Several self-report instruments for ASD and other disorders are available, but their validity is questionable because of their low specificity.[28–30]

ASD in adulthood

Estimates vary, but 10–33% of adults with ASD do not use more than simple phrases and have verbal and non-verbal IQs in the range of intellectual disability, requiring very substantial support.[21,26,31] Most adults with ASD with intellectual disability can speak at some level, can take care of basic needs, and have the ability to work, but need daily support. Premature mortality is increased, primarily in individuals with lower intellectual abilities and in women (mostly resulting from congenital abnormalities and neurological disorders), but also in more able people with comorbid diagnoses.[32,33]

In a community sample (ie, not a clinic sample), about a third of adults who were diagnosed with ASD as children and had average or higher intelligence no longer had obvious ASD features, although many had minor psychiatric conditions.[34] Thus, there is a wide range of adult outcomes. However, finding appropriate employment and services is difficult. Although a study published in 2013 showed that educational attainments had improved compared with 20 years earlier,[35] employment did not generally match levels of education. In terms of independence, in the USA, only about 25% of individuals with ASD with average intelligence live in their own households,[34] with the remainder living with their families into at least middle age. Marriage and long-term intimate relationships are still rare. The proportion of people with at least one reciprocal friendship in the past 20 years increases during childhood and adolescence for more able individuals with ASD, but remains lower than that in the general population.[35] However, we have almost no knowledge of characteristics of adults with ASD outside the USA and Europe.

Adults seeking first diagnoses of ASD typically are not intellectually disabled and often have comorbid psychiatric conditions.[31] Notably, the proportion of adults formally diagnosed with ASD after attending an ASD clinic is lower than that of children; this is perhaps because people with the clearest ASD symptoms have already been diagnosed.[31] Brief self-report measures do not have adequate specificity, but versions of the ADOS, the 3di, and the SRS are appropriate for verbally fluent adults.[36–38] Other general psychiatric diagnostic measures and a developmental history from relatives, if approved by the patient, can be helpful,[39] and a general cognitive assessment including verbal and non-verbal scores is also important. There is concern that women are under-diagnosed and diagnosed later because of the belief that ASD primarily occurs in male individuals or because it is masked by female gender-related social differences.[40] Co-occurring difficulties (eg, depression or severe anxiety) can cause as much impairment as ASD features.[39]

Several self-advocacy and identity movements are associated with ASD. These movements generally emphasise respect for neurodiversity, strengths (such as attention to detail), and individual differences, and have called for ASD to be considered a condition rather than a disorder. By contrast, parents of less able people with ASD have expressed concern that the predominant media focus on the most intelligent individuals with ASD, and the argument to consider ASD as an aspect of neurodiversity, downplays the impairments of those children and adults with the greatest needs and diminishes the importance of their voices also being heard.[41]

Co-occurring psychiatric conditions in ASD

Clinicians have long been aware that ASD is often accompanied by other difficulties. In addition to ASD, the earliest considerations are usually developmental delay or intellectual disability, and language and motor difficulties. DSM-5 recognises this complexity by allowing multiple diagnoses, even within psychiatry, such as ASD and ADHD.

ADHD is the most common comorbidity in people with ASD (28·2% [95% CI 13·3–43·0]), [42] and considerably affects outcomes in children with ASD who have average intelligence or intellectual disability.[43] How ADHD affects children and adults changes over time in terms of interactions with executive functioning, peer relations, and depression, and should therefore be monitored.[43]

Anxiety in various different forms—including social anxiety, generalised anxiety, separation anxiety in younger children, and phobias—also affects many children with ASD.[42,44] Anxiety and depression are more common, or at least more observable, in verbally fluent individuals, and increase during adolescence in girls, while also occurring in a substantial minority of boys.[45]

Irritability and aggression are more common in ASD (25%) than in other developmental disorders (eg, idiopathic intellectual disability), although they take many different forms from minor physical aggression in very young children to verbal aggression in adults.[46]

Trajectories and predictors of outcome

The range of outcomes, from individuals who remain non-verbal to those able to work and live independently without continuing ASD symptoms, greatly increases uncertainty for families and pressure on parents to get the most out of each intervention. Diagnoses of ASD can be made in children as young as 15–24 months in some cases, although these early diagnoses should be monitored closely.[47] The greatest gains, even into adulthood, are made by children who have begun to make progress in language and have about average non-verbal skills by 3 years of age.[48] Changes in language after age 5 years tend to be linear; changes before that age can include more dramatic shifts in trajectories that result in catching up to overall age-group average levels,[48] whereas those who do not catch up can be identified as having intellectual disabilities.

By age 9 years, friendship and engagement with peers, often associated with access to integrated school programmes, predicts adult outcome in terms of independence and

decreased symptoms, as do stronger adaptive skills.[49] In a longitudinal study,[34] parent participation in early intervention for children between 2 and 3 years of age, even in as few as 20 sessions in a year, consistently predicted more positive adult outcomes in terms of increased IQ (d=0·5), achievement (d=0·33), and adaptive skills (d=0·27) in both less cognitively able and more cognitively able young adults (mean age 19 years), and also increased the probability of full independence in more able individuals, although this could reflect parent motivation and resources as much as treatment.[34]

Descriptive epidemiology

A 2012 review commissioned by WHO estimated that the global prevalence of ASD was about 1%,[50] with a more recent review estimating the prevalence to be 1·5% in developed countries.[51] Increases in prevalence estimates in the USA over the past several decades have now mostly plateaued[21] and probably can be largely accounted for by improved awareness and services, differences in documentation, and the inclusion of milder cases without intellectual disability.[52] Only two rigorous studies of adult epidemiology of ASD have been done, both in the UK, and also provided estimates of about 1%, with many adults never having received a formal diagnosis.[28,39]

Environmental risk factors

Many risk factors for ASD have been suggested. A number of systematic reviews and meta-analyses have described prenatal and perinatal factors, as well as maternal dietary and lifestyle factors.[53] The immediate practical implications of most environmental factors for families hoping to minimise their risk with a subsequent child (after already having a child with ASD) are so far limited to the identification of likely-causal genetic anomalies in a minority of cases.

Advanced maternal age (≥40 years) and paternal age (≥50 years)[54] have been independently associated with ASD risk in several studies,[51] as have short interpregnancy intervals (<24 months).[55] Non-specific non-optimal factors during pregnancy, including maternal metabolic conditions, weight gain, and hypertension, as well as more specific factors (such as maternal admission to hospital due to bacterial or viral infections, or familial history of autoimmune disease) have also been associated with a mildly increased risk of ASD and developmental delay combined.[56]

Several studies have investigated maternal medication use during pregnancy. Prenatal valproic acid exposure has been associated with increased risk of ASD.[57] For antidepressants, including selective serotonin-reuptake inhibitors, well controlled studies[51,58] have suggested no unequivocal risk, despite earlier concerns.

Preterm birth (<32 weeks), low birthweight (<1500 g), small-for-gestational-age status,[59] and large-for-gestational-age status (>95th birthweight percentile)[60] have been independently associated with an increased risk of ASD, although whether these factors are causal or markers of risk is unclear.[51] Nevertheless, these children should be monitored for ASD during later infancy and early toddler years. No consistent associations between caesarean delivery or assisted conception and risk of ASD have been found.[51]

Preconceptual folic acid supplements have been associated with a decreased risk of ASD and general developmental disabilities, with a significant gene–environment interaction.[61] Some links with air pollutants and maternal stressors during pregnancy have been found, but variable methods and results across countries make interpretations difficult.[51] Associations between ASD and vaccinations have been sought multiple times and not found.[62]

ASD and paediatric conditions

ASD is strongly associated with numerous coexisting conditions—physical, mental, neurodevelopmental, and functional—that are not part of the diagnostic criteria but can nevertheless have a substantial, often negative, effect on the wellbeing of the child or young person and their family, and can require modification of intervention strategies. Coexisting conditions vary in prevalence depending on the population studied, but include other neurodevelopmental disorders, intellectual disability (IQ <70; prevalence 15–65% for different samples),[24,63] and academic learning difficulties (75% of individuals aged 9–18 years with ASD had at least one area of literacy or mathematical achievement highly discrepant from their general intellectual ability, with reading comprehension most often being low).[64,65] The prevalence of speech and language delays is estimated to be 87% in 3-year-old children with ASD.[66,67] Other conditions include tics (in 9% of preschool and school-age children),[42] sleeping problems (25–40%),[68,69] restricted and rigid food choices (42–61%),[70] obesity (23%),[71] gastrointestinal symptoms (47%),[72] and elimination problems, particularly bowel evacuation and constipation (12%).[73] Epilepsy has a reported prevalence of 8·6% in people with ASD and is particularly associated with intellectual disability and female sex.[74] Common coexisting conditions (eg, problems with sleeping, picky eating, and toileting) should be systematically investigated and treated; often, approaches like those used for children without ASD can be used and are similarly effective in children with ASD, although somewhat more creativity and persistence is needed.

Genetics

The past decade has seen a shift from a general concept of genetic risk to more specific attention to a large number of heterogeneous, individual genetic variants associated with ASD risk. The shifting definitions of ASD have led to variable rates of diagnosis in twin and family studies. A meta-analysis published in 2016 reported that 74–93% of ASD risk is heritable,[75] although non-genetic factors are also important. Sibling studies indicate that ASD occurs in 7–20% of subsequent children after an older child is diagnosed with ASD,[76,77] and this prevalence is increased in children with two older siblings with ASD. Risk is 3–4-times higher in boys than girls.[78] Models of genetic risk in ASD favour complex inheritance, with additive contributions from common variants that individually make small contributions to risk,[79] as well as rare variants that have larger effect sizes but are still not deterministic causes of ASD.[80] Relative to rare variants, common risk variants have been difficult to identify because of overlap with the general population.

The first evidence for specific genetic risk factors in ASD arose in rare genetic syndromes, such as fragile X syndrome[81] and tuberous sclerosis,[82] which include ASD in some children. However, the most common of these syndromes, fragile X syndrome, is present in less than

2% of children with ASD. Genomic copy-number variants, in which a chromosomal subregion is duplicated or deleted, can be inherited or occur de novo (ie, in the child but not in either parent). In ASD, copy-number variants are best considered as risk variants rather than causal mutations, because most lead to ASD in a minority of children and can also be found in people with other developmental disorders or without any diagnosis. A few variants are common enough that their associated features have been individually studied, such as chromosome 16p11.2 deletions and duplications[83] and maternal 15q11–q13 duplications.[84]

In the past 15 years, recurrent, de-novo, likely gene-disrupting, single-nucleotide variants have been identified in more than 100 genes, some of which also harbour rare, inherited single-nucleotide variants that appear to contribute to ASD risk.[85] The most common gene disrupted by these rare, de-novo events is *CHD8*,[86] although such variants are found in less than 0·5% of children with ASD. The collection of implicated genes seems to be enriched for certain biological functions including neuronal function and regulation of gene expression, suggesting common pathways that lead to ASD risk.[87,88]

Many physician organisations now recommend that every child with ASD receive genetic testing, including fragile X syndrome testing and a chromosomal microarray to detect copy-number variants.[89] Some clinicians in North America and Europe already order whole-exome or whole-genome sequencing for children without chromosomal microarray findings. Sequencing could soon become the standard of care for ASD in some countries. Although testing can be ordered by any physician, referral to a specialist such as a clinical geneticist is typically indicated for children with specific genomic findings.

Currently, genetic testing has the potential to improve family planning (and provide a medical explanation for a child's ASD in some cases), trigger screening for co-occurring medical problems, aid prognostication, and connect families to specific support groups. Treatment studies are underway in some children with genetically defined syndromes, such as fragile X syndrome. Within the next decade, we expect that genetic research will allow the development of new treatments for some children.[85]

Neurobiology

In neurobiology, ASD is no longer viewed as a focal impairment in a specific brain region or system, but instead as a condition resulting from overall brain reorganisation beginning early in development. Among the most well replicated findings is a pattern of overgrowth of brain volume in infancy and early childhood, as documented through differences in brain volume on neuroimaging.[90,91] Relative to typically developing children, those with ASD have accelerated brain development early in life, which results in altered connectivity.[92] Connectivity is a broad concept encompassing physical inter-connections as well as correlations or causal interactions in activity of different regions. Findings are generally consistent in showing a pattern of overall brain under-connectivity, coupled with local over-connectivity within specific regions,[5,93] often the frontal and occipital regions. Given that the underlying cellular mechanisms for these neural patterns in early development are yet to be understood, we do not have strong evidence for how altered connectivity differentially

affects specific brain regions, measurements (eg, brain volume [grey *vs* white matter], cortical thickness, gyrification), and conditions (eg, recording parameters or tasks).[5,91]

Research on altered brain development and functioning has further elucidated differences in sensitivity to the environment and distinct styles of learning, which in turn lead to brain reorganisation during development, resulting in heterogeneous profiles in adults with ASD. Subtle alterations in multiple brain systems subserving social and attentional mechanisms are observed well before the emergence of overt behavioural symptoms.[94] These alterations sometimes remain stable into adulthood, as different individuals use adaptive and compensatory mechanisms to address their challenges. Although it was hoped that head circumference might offer an informative biomarker for measuring individual variation in brain growth over time, it has been shown to have little usefulness as a predictor of ASD.[95] Given the complexity and uncertain nature of the causes of ASD, there is a need to provide families and other caregivers, especially around the time of diagnosis, with accurate information about biological differences that might underlie their child's behaviour or different styles of learning.

Treatment

How much and what kind of intervention children and adults with ASD receive vary immensely across the world and even within countries and regions.[94] One consistent finding across many (although not all) locations is that parents with a lower educational level are less successful in obtaining specialist interventions that could improve outcomes. In one survey about European services for less well educated families, even low-cost and publicly funded interventions were not available to children until a year after diagnosis.[96]

Early parent-mediated interventions

Several well designed randomised controlled trials have shown that low-intensity interventions that coach parents on how to interact with their young children with ASD can result in immediate effects on children's social behaviour and communication.[16] These treatments emphasise teaching parents and caregivers to establish joint engagement, avoid being very directive, and create opportunities for shared attention and balanced play so that children gradually take more initiative.[16] The treatments can also help, to some degree, to alleviate the distress of families and give them something positive to focus on.[97]

These treatments tend to be non-intrusive for families, relatively low in cost, adaptable for the clinic or home and for groups or individuals, and could be helpful even for families of very young at-risk children who, in the end, might not develop ASD but have other delays. Formal treatments that fit into the category of early parent-mediated interventions are listed in panel 2. All have shown some effectiveness, with variations in intensity and duration (effect sizes for early parent-mediated interventions are typically around d=0·30).[98] One paper showed these that the benefits of these interventions lasted beyond early years and into later childhood (effect size 0·70).[103]

However, other studies with similar low-intensity approaches (eg, More Than Words) have not shown positive results, and non-specific factors might influence the effects.[99,104]

Furthermore, no formal studies have directly varied the intensity of interventions or contrasted one approach with another. Strategies that work for most children might not work for everyone; for children with severe delays who cannot yet play or manipulate objects well, teaching their parents to avoid initiating play or other interactions might not be helpful.[66] Similarly, although most children learn words first receptively and then expressively, children with substantial delays might learn words first by saying them and then come to understand them.[66] Thus, not all children with ASD will benefit from the same approaches.

Naturalistic behavioural developmental interventions

The treatment that has received the most attention historically in North America has been early intensive behavioural intervention. The most well known form of this treatment is Applied Behaviour Analysis (ABA), but there are many versions of this approach. A 2015 review[100] summarised the research on these approaches and introduced the term naturalistic developmental behavioural interventions (NDBI), which includes Pivotal Response Treatment (PRT), Early Start Denver Model (ESDM), Joint Attention Symbolic Play and Engagement Regulation (JASPER), and Early Social Interaction (ESI) (panel 2). These treatments differ from one another but share similarities in that they follow typical developmental sequences more closely as compared with the original ABA protocols; they emphasise play, social interaction, and communicative initiation on the part of the child, and natural consequences as opposed to rewards such as food. These treatments are generally undertaken by an adult teacher or therapist working one-to-one with a child, using principles of learning to teach a child developmental skills such as language, imitation, or cognitive tasks such as matching or sorting. The treatment is usually intended to be given intensively in periods of 15–20 h or more per week. Meta-analyses of treatment studies[16,105] report effect sizes of d=0·69 for adaptive skills, d=0·76 for IQ, and about d=0·50 for language skills after 2 years of treatment; however, only one trial was truly randomised and all studies compared the NDBIs to a treatmentas-usual control group. When NDBI approaches have been directly compared with other developmental approaches of equal intensity, no difference has been found.[16] Another commonly used treatment that also uses modified behavioural techniques is TEACCH (Treatment and Education of Autistic and Communication Handicapped Children and Adults),[106] which is a way of using the temporal and physical environment to increase independence, communication, and predictability, often within a classroom setting.

Overall, parent-mediated interventions primarily affect social communication interaction and sometimes ASD symptoms over time; one-to-one (adult and child) intensive interventions based on NDBI or ABA have been shown to affect language development, cognition, and adaptive skills, perhaps because they are usually more intense, structured treatments. Children might benefit in different ways from both social communication-oriented parent-mediated interventions and direct one-to-one treatments from therapists or teachers;[107] however, we do not yet have research to guide these decisions.

Many other interventions are available to children with ASD, some routinely through schools or health systems and some sought out by parents. Although specific techniques within speech therapy have general empirical support, it has been difficult to show that

speech therapy and occupational therapy are effective, in part because they represent many different treatments. In general, techniques in speech therapy have been shown to increase spoken single-word acquisition and improve simple sentence structure, but shown no effects on complex language so far.[107]

Sensory-oriented treatments are a considerable part of early interventions and school-based treatments in North America, but are less so in other countries. A small amount of research literature is accumulating, with the same limitations as other behavioural studies in terms of small samples and various risks of biases. Sensory-integration approaches delivered by occupational therapists improved sensory and motor skills in the short term (d=0·12 to d=1·2 for teacher and parent ratings and sensory evaluations) compared with usual care in young children.[108] Auditory-integration treatments have not yielded consistently positive results. Music therapy results have been generally positive, although limitations in the study designs mean that conclusions should be made with caution. General environmental stimulation improved cognitive skills in two small-scale studies. Various sensory-related components (eg, weighted blankets, swings, or brushing) have not shown consistent positive effects, except perhaps massage (d=0·6 to d=0·7 for self-regulation and sensory responses).[109]

Behavioural and social treatments for school-age children, adolescents, and adults

For school-age children and adolescents, the most common behavioural interventions are social skills groups. Numerous highly manualised programmes in which children, adolescents, and parents participate separately and together have been shown to result in improvements in social behaviour (d=0·98 for selfreported social skills; d=0·58 for tasks; smaller effects for parent and teacher reports) in randomised controlled studies.[110] A variety of other manualised programmes emphasise different components, such as executive functioning, theory of mind, and more comprehensive approaches, such as SCERTS (Social Communication/Emotional Regulation/Transactional Support), with less strong empirical support.[111] Social stories (a strategy in which a caregiver depicts an anticipated or experienced event in cartoons and the child and adult then discuss it) have also been shown to reduce disruptive behaviour.[112]

Many of these programmes use cognitive behavioural therapy as their underlying theoretical framework. A number of group therapy programmes have aimed to reduce anxiety symptoms in children with ASD, usually with parallel parents' and children's groups.[113,114] The frequency of anxiety symptoms in ASD attests to the important need for such interventions.[42] These approaches usually last about 3 months and report quite high effect sizes (d>0·70), with about half of children in the therapy groups responding compared with less than 10% of those in control groups.[115] Effects of behavioural interventions on depression have been more difficult to document.[116]

A manualised treatment called parent-child interaction therapy increased shared positive affect and child adaptability,[117] consistent with the general finding that hands-on parent training reduces disruptive behaviour more than parent education alone (effect sizes d=−0·62 to d=0·70).[118] Interventions for aggression and oppositional disorders remain an

underserved need for many families of children with ASD, and traditional behaviour management can help.[42] An ongoing debate is whether new behavioural descriptions, such as pathological demand avoidance[119] (a term of rising popularity in the UK), are helpful or harmful, particularly when they are primarily based on questionnaires or non-specific items from caregiver reports. There are many unknowns about how best to consider the complexity of the associations between the deficits of ASD, emotional regulation, and existing diagnoses (such as oppositional defiant disorder) and other behavioural difficulties.[120]

Few studies have investigated behavioural treatments in adults, except those for anxiety and depression discussed earlier. This area warrants more research, moving beyond cognitive behavioural therapy and social skills groups to include broader life skills and, for example, anger management and self-advocacy, as well as medical issues such as obesity.[19] Another area of focus has been how to increase employability in adults with ASD, with an emphasis on helping secondary school students and young adults to enter community-integrated programmes as soon as possible, rather than practising work in special workshops or schools.[121]

Another area of concern is the disparity in services—in terms of availability, quality, and utilisation—across racial and ethnic groups and between families with different levels of educational and financial resources. Research showed that services such as family peer advocates (who focus on families' involvement rather than a more medical or traditional therapeutic perspective) increase knowledge and decrease stress for underserved populations,[122] but with no change in use of services. The increasing prevalence of ASD in the USA among diverse populations suggests improved identification of the disorder, but the same information is not available about the dissemination of treatments and educational approaches. Concerns about appropriate services and accurate diagnoses for girls and women with ASD have also received increasing attention recently. Although ASD is consistently more prevalent in male individuals, estimates of sex ratios vary markedly across populations,[50] as do patterns of symptoms, interacting with differences in distributions of intelligence, motor skills, and known genetic factors.[117]

Pharmacology

Evidence-based pharmacology in ASD is currently limited to the treatment of co-occurring behaviours or diagnoses, not ASD itself. Risperidone[123] and aripiprazole[124] have improved symptoms of irritability or agitation in children and adolescents with ASD in randomised controlled trials. Overall, with use of these two medications, the majority of (but not all) children show improvement in irritability and agitation, which includes aggression, self-injury, and other disruptive behaviours.[125] Both drugs are mixed dopamine-receptor and serotonin-receptor antagonists or partial agonists, and are in a class commonly termed atypical antipsychotics. Not all similar medications are helpful in ASD.[126] Both drugs can also cause adverse events, including sedation and weight gain, increasing risk of later health problems. Metformin is helpful in ameliorating weight gain due to these medications in ASD.[127]

A few medications typically used to treat ADHD, including methylphenidate,[128] atomoxetine,[129] and guanfacine[130] (table), also show benefit for ADHD symptoms in ASD, which occur in over a quarter of children.[42] Each of these drugs yields less benefit and more adverse events in individuals with ASD than in the general ADHD population. The available studies suggest that these three drugs should be limited to use in children with ASD who have co-occurring ADHD, which is made as a separate diagnosis according to DSM-5.

Children with ASD and co-occurring epilepsy or other neurological disorders should be treated on the basis of evidence in children without ASD.[131] It is reasonable to similarly adapt evidence from the general paediatric population for the treatment of mental illnesses that co-occur with ASD, such as anxiety and mood disorders. To date, despite the frequent co-occurrence of epilepsy, anxiety disorders, and mood disorders with ASD, no randomised controlled trials have evaluated whether medications for these co-occurring disorders show similar response rates or adverse events in people with ASD. Caution should therefore be used, with preference for lower-risk treatments, including behavioural or psychosocial interventions.

Some clinicians, including those who describe their practices as biomedical or holistic, prescribe various treatments that have no evidence and no biological plausibility in ASD.[132] A few supplements, such as sulforaphane[133] and folic acid,[134] have some biological plausibility and some pilot evidence, but further study is needed. Care should be taken to avoid harm associated with certain non-evidence-based treatments, such as toxicity due to chelating agents or hyperbaric oxygen.[135] Clinicians should prevent these treatments from distracting or diverting resources from evidence-based behavioural or educational interventions.

Future directions

Given existing health systems, there are clear, continuing needs for coordination between health-care, education, and other services (such as intense support for challenging behaviours and planning for adult residential and employment programmes for individuals with ASD). Even the immediate demand on physicians' time for counselling and support of families facing potential early diagnoses is a controversy in the USA because these are generally not billable services for paediatricians. To date, scientific focus has primarily been on the development of more accurate tools for identification; however, using community resources to develop and promote use of more readily available treatment programmes in which young children and adults can participate might make more sense, because physicians are more likely to screen and refer when they perceive a benefit to the family from doing so. Economic data—such as a 2012 report that indicated that, in the USA, for every $1000 spent on respite care, there was an 8% decrease in spending on inpatient psychiatric services on Medicaid-enrolled children with ASD[136]—could be helpful in justifying the cost of services such as respite care.

In basic science research, much has been learned; however, the clinical implications remain few, partly because of findings from both genetics and imaging studies that ASD is not typically caused by a specific gene or highly localised lesion, but might result from

combined or not-yet-understood genetic risks and disruptions in very early developing neural pathways. Although the idea of continuous traits underlying ASD is appealing to many scientists, it should also be recognised that many of these traits, such as intelligence, language level, activity level, anxiety, motivation, and aggression, interact with each other in complex ways, and thus simple models do not represent actual development.

In terms of global health, focusing on the goals of children and adults with ASD and their families, rather than on how to plug gaps in existing systems, might help to set appropriate priorities. Innovative solutions, such as adaptations of evidence-based interventions for low-resource settings through empowering front-line health-care workers, are underway.[137,138]

Conclusions

Life for many children and adults with ASD is improved today compared with 50 years ago. More adults with ASD can talk, read, drive, graduate from school, and live in the community —even accounting for the differences in which people would meet the diagnostic criteria now and in the past, and their respective levels of intelligence. Caregivers can be reassured that the situation has improved, and will continue to improve, for most people with ASD. We hope that research directs attention to individuals who still have substantial difficulties and provides pathways to fuller inclusion and greater independence for more people. Science and public policy both have the potential to contribute to such changes. Working with families, schools, and community providers, clinicians can make differences in the lives of individual children and adults by providing accurate and realistic information, support, and hope.

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Search strategy and selection criteria

Initial searches were done on Aug 14, 15, and 17, 2017. Additional searches were done on Feb 21–23 and March 18–21, 2018. Searches were limited to the English language. To identify studies for this Seminar, we searched PubMed and individually searched the Cochrane database, and followed back by searching reference lists of papers cited in major journals for papers published between 2007 and 2017, using the search terms "autism behavioral treatment", "autism diagnosis", "autism environmental factors", "autism epidemiology", "autism incidence", "autism prevalence", "autism risk factors", "autism spectrum disorder behavioral treatment", "autism spectrum disorder diagnosis", "autism spectrum disorder environmental factors", "autism spectrum disorder epidemiology", "autism spectrum disorder incidence", "autism spectrum disorder risk factors", "autistic disorder behavioral treatment", "autistic disorder diagnosis", "autistic disorder environmental factors", "autistic disorder epidemiology", "autistic disorder incidence", "autistic disorder prevalence", "autistic disorder risk factors", "Asperger's syndrome behavioral treatment", "Asperger's syndrome diagnosis", environmental factors", "Asperger's syndrome epidemiology", "Asperger's syndrome incidence", "Asperger's syndrome prevalence", "Asperger's syndrome risk factors", "Asperger's disorder behavioral treatment", "Asperger's disorder diagnosis", "Asperger's disorder environmental factors", "Asperger's disorder epidemiology", "Asperger's disorder prevalence", "Asperger's disorder risk factors", "pervasive developmental disorder behavioral treatment", "pervasive developmental disorder diagnosis", "pervasive developmental disorder environmental factors", "pervasive developmental disorder epidemiology", "pervasive developmental disorder incidence", "pervasive developmental disorder prevalence", "pervasive developmental disorder risk factors", "PDD-NOS behavioral treatment", "PDD-NOS diagnosis", "PDD-NOS environmental factors", "PDD-NOS epidemiology", "PDD-NOS incidence", "PDD-NOS prevalence", "PDD-NOS risk factors". Only articles published in English were included. We also examined key recent reviews and book chapters. To reduce the number of papers cited, the most up-to-date review papers and meta-analyses were used when possible. We selected papers according to our judgment of the quality of the study or review paper, the relevance to controversial or commonly misunderstood issues, and whether findings had clinical relevance. We included older papers that we judged to be important.

Panel 1: Signs and symptoms of autism spectrum disorder as described in DSM-5 (299.0)[6]

Persistent deficits in social communication and social interaction across multiple contexts, as manifested by

- Deficits in social–emotional reciprocity (eg, abnormal social approach and failure of normal back-and-forth conversation; or reduced sharing of interests, emotions, or affect)
- Deficits in non-verbal communicative behaviours (eg, poorly integrated verbal and non-verbal communication, abnormalities in eye contact and body language, or deficits in understanding and use of gestures)
- Deficits in developing, maintaining, and understanding relationships (eg, difficulties adjusting behaviour to suit various social contexts; or difficulties in sharing imaginative play or making friends)

Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by

- Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys, or flipping objects)
- Insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal and non-verbal behaviour (eg, extreme distress at small changes, difficulties with transitions, or rigid thinking patterns)
- Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects)
- Hyperreactivity or hyporeactivity to sensory input, or unusual interests in sensory aspects of the environment (eg, apparent indifference to pain or temperature, or adverse responses to specific sounds or textures)

Notes on diagnosis

- Individuals with a well established DSM-IV diagnosis of autistic disorder, Asperger syndrome, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder
- Symptoms must be present in the early developmental period (but might not become fully manifest until social demands exceed limited capacities, or might be masked by learned strategies in later life)
- Individual must have social communication deficits (past or present) in each of the three areas defined above
- Individual must have two of the four restricted, repetitive patterns (past or present), as defined above
- Symptoms must cause clinically significant impairment in social, occupational, or other areas of current functioning

Panel 2: Early parent-mediated treatments and early naturalistic developmental behavioural interventions with evidence for treatment, and parent-friendly online resources

Early parent-mediated treatments

- Developmental Individual-Difference Relationship-Based Model (DIR) or Floortime[98]
- Early Social Interaction (ESI)[23]
- Early Start Denver Model (ESDM)[99]
- Joint Attention Symbolic Play Engagement and Regulation (JASPER)[100]
- Preschool Autism Communication Trial (PACT)[101]

Early naturalistic developmental behavioural interventions

- Early Achievements[100]
- Enhanced Milieu Teaching (EMT)[100]
- Early Start Denver Model (ESDM)[99]
- Incidental Teaching (IT)[100]
- Joint Attention Symbolic Play Engagement and Regulation (JASPER)[100]
- Pivotal Response Treatment (PRT)[100]
- Project ImPACT (Improving Parents As Communication Teachers)[100]
- Reciprocal Imitation Training (RIT)[100]
- Social Communications/Emotional Regulation/Transactional Support (SCERTS)[102]

Parent-friendly and client-friendly websites

- American Academy of Child and Adolescent Psychiatry (https://www.aacap.org/aacap/families_and_youth/resource_centers/autism_resource_center/home.aspx)
- American Academy of Pediatrics (https://www.aap.org/en-us/pages/default.aspx)
- Assessment, Diagnosis, and Interventions for Autism Spectrum Disorders (http://www.sign.ac.uk/assets/sign145.pdf)
- Australian Autism CRC (https://www.autismcrc.com.au/)
- Autism Alliance (https://www.autism-alliance.org.uk/)
- Autismo Diario (https://autismodiario.org/)
- Autism Speaks (https://www.autismspeaks.org/)

- Autism Spectrum Disorder in Adults: Diagnosis and Management (https://www.nice.org.uk/guidance/CG142)
- Autism Partnership (https://www.autismpartnership.com/)
- Autistic Self Advocacy Network (http://autisticadvocacy.org/)
- Centers for Disease Control and Prevention (https://www.cdc.gov/ncbddd/autism/index.html)
- Confederación Autismo España (http://www.autismo.org.es/AE/default.htm)
- Florida State University Autism Navigator (http://med.fsu.edu/index.cfm?page=autisminstitute.autismnavigator)
- National Institutes of Health (https://search.nih.gov/search?utf8=%E2%9C%93&affiliate=nih&query=autism+and+parents&commit=Search)

Table:

Evidence for use of medication in autism spectrum disorder

	Age (years) for use as indicated by US FDA	Target symptoms	Effect size (d)	Common adverse effects
Risperidone	5–16	Agitation or irritability in ASD	0.94[123]	Increased appetite, sedation, weight gain
Aripiprazole	6–17	Agitation or irritability in ASD	0.87[124]	Nausea, weight gain
Atomoxetine	6–15	Typically for ADHD symptoms	0.68–0.84[129]	Decreased appetite nausea, irritability
Methylphenidate	≥6	ADHD	−0.78 (95% CI −1.13 to −0.43) (teacher-rated)[128]	Sleep disruption, decreased appetite
Guanfacine	6–12	ADHD	1.67[130]	Fatigue, sedation, decrease in pulse and blood pressure

ASD=autism spectrum disorder. ADHD=attention-deficit hyperactivity disorder. FDA=US Food & Drug Administration.