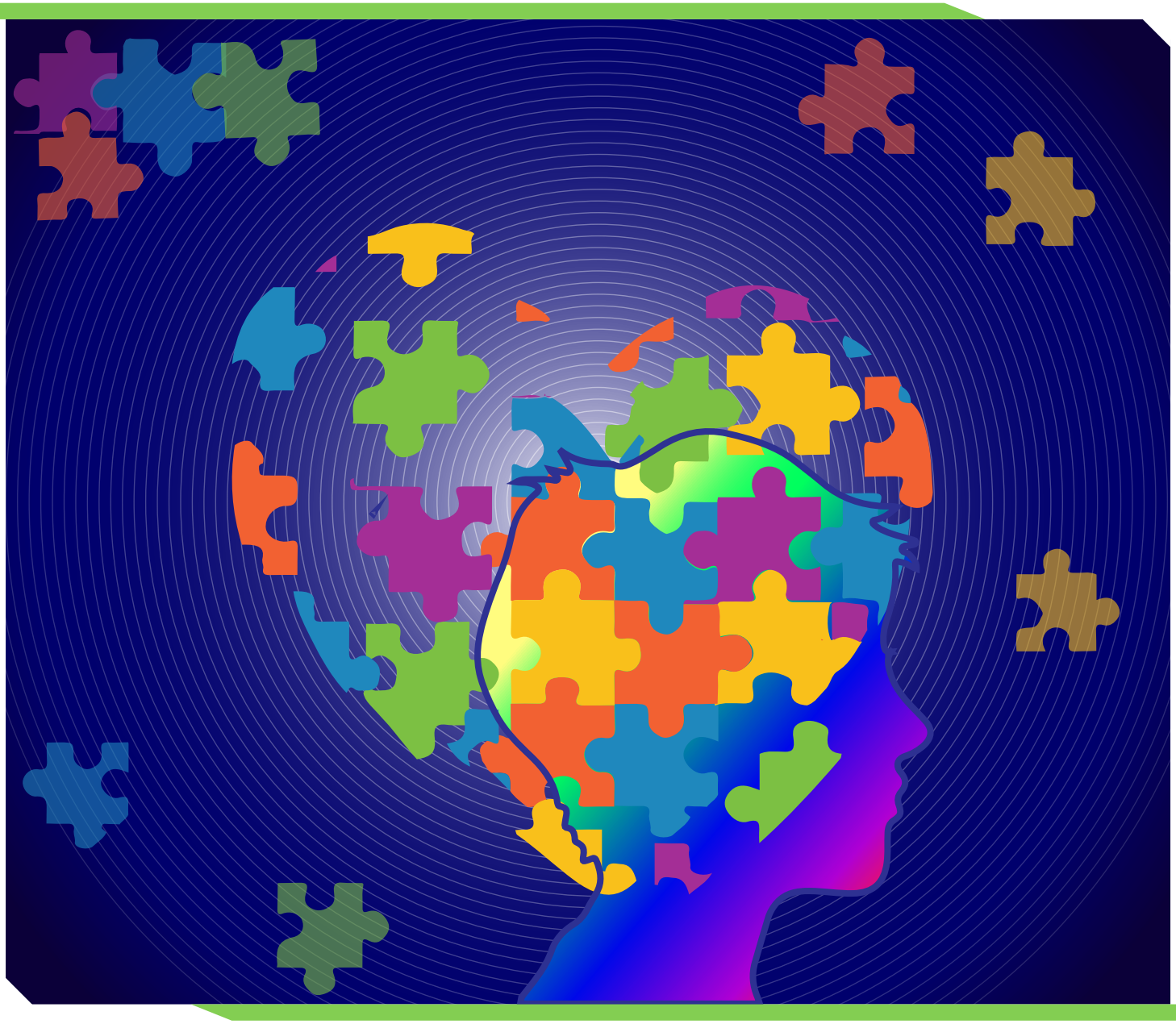
AUTISM :
THE LATEST STORY



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AUTISM: The Latest Story

ANCC Accredited NCPD Hours: 2.3hrs

Target Audience: RN/APRN

Need Assessment

Autistic Spectrum Disorder (ASD) is a complex neurodevelopmental brain disorder characterized by two core behavioral symptoms, namely impairments in social communication and restricted/repetitive behavior. Recent genetic and non-genetic models contributed significantly in understanding the pathophysiology of ASD, as they establish autism-like behavior. ***Among the genetic causes, several chromosomal mutations including duplications or deletions could be possible causative factors of ASD.*** In addition, the biochemical basis suggests that several brain neurotransmitters, e.g., dopamine (DA), serotonin (5-HT), gamma-amino butyric acid (GABA), acetylcholine (ACh), glutamate (Glu) and histamine (HA) participate in the onset and progression of ASD. Despite of convincible understanding, risperidone and aripiprazole are the only two drugs available clinically for improving behavioral symptoms of ASD, approved by Food and Drug Administration (FDA). Till date, there is no other drug approved for clinical usage specifically for ASD symptoms. However, many novel drug candidates and classes of compounds are underway for ASD at different phases of preclinical and clinical drug development.

Objectives

- Discuss the variations in intellectual functioning in children with autism
- Describe the early emergence of autism features
- Identify the differential diagnosis of autism and global developmental delay
- Describe the impact of developmental level on the presentation of autism symptoms
- Discuss the recent global prevalence estimates of autism

Goal

The goal of this article is to discuss the prevalence, incidence, diagnosis, latest guidelines on treatment of autism group of disorders in children

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by early impairments in socialization and communication, as well as restricted interests and repetitive behaviors. Currently, the Center for Disease Control and Prevention (CDC) estimate that one in every 59 children has ASD; although most children are diagnosed by age 3 years, approximately 39% are not evaluated for the first time until after age 4 years.

There is clear evidence that ASD-specific symptoms emerge in the first 2 years of life, however, a large proportion of affected children (i.e., up to 87.5%) exhibit both behavioral and neurological signs of ASD prior to their first birthday. Even so, ASD can be difficult to diagnose in very young children, as many of the defining characteristics (e.g., peer-peer relationships, lack of conversation skills, and restricted or stereotyped interests) are age-or development-specific. That is, these behaviors are not usually seen in infants and young toddlers, nor are they seen in older individuals with low mental age (low MA), defined as developmental functioning below a 12-month level. Despite these challenges, ***it is possible to diagnose ASD in children with low MA, and these diagnoses show high stability over a 2-year period. To facilitate diagnosis and intervention early in development, it is important to understand how ASD manifests in very young and cognitively delayed children.*** [1, Rank 5]

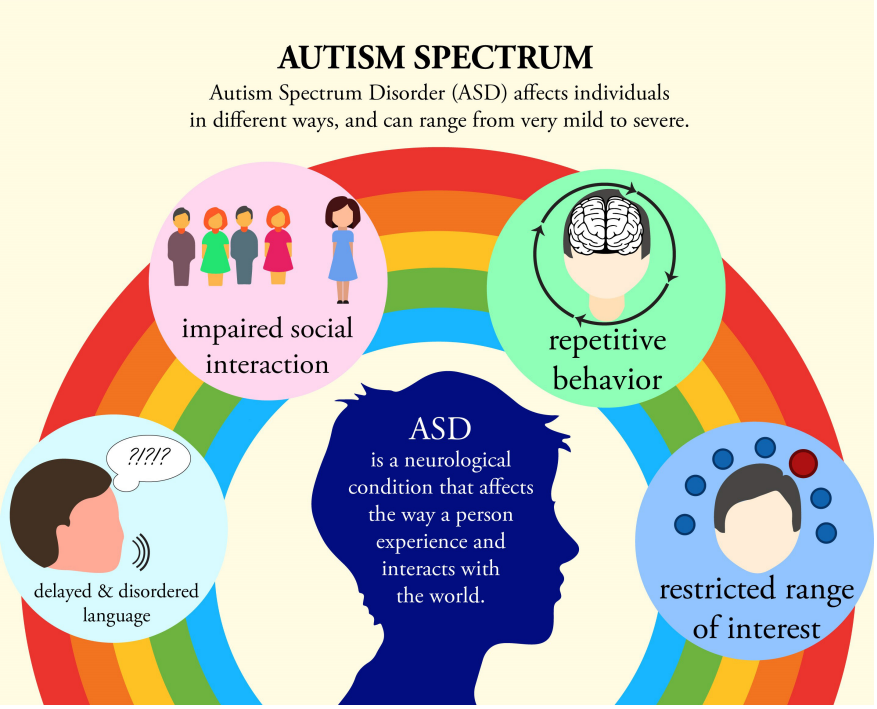

Figure 1: Autism Spectrum Disorder

Figure 2: children and Autism Spectrum Disorder

Variations in Intellectual Functioning in Children with Autism

Variations in intellectual functioning contribute to the challenge of diagnosing ASD. Current estimates suggest that the prevalence of ***comorbid intellectual disability (ID, defined as IQ ≤ 70)*** in individuals with ASD is approximately 31%. Further, the percentage of children for whom developmental concerns are raised before age 3 years is significantly higher in children later diagnosed with comorbid ASD and ID, as compared to individuals diagnosed with only ASD, suggesting that children with comorbid cognitive delays may be a particularly severe subgroup. Cognitive functioning is an important predictor of response to intervention and functional outcomes in individuals with ASD.

In particular, children with ASD and comorbid cognitive delays appear to make limited developmental progress

> **"Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by early impairments in socialization and communication, as well as restricted interests and repetitive behaviors."**

over time and show greater deficits in adaptive functioning, social skills, and disruptive behavior even with intensive intervention, perhaps suggesting that those with low MA may struggle to respond to traditional ASD specific intervention services. ***Intellectual level can be difficult to measure accurately in very young children because developmental domains may undergo rapid changes in early childhood, and because the children may have difficulty complying with the demands of testing.*** Given that children with ASD and low MA may require more intensive or adapted intervention approaches, however, it is necessary to assess possible intellectual impairment in toddlers with ASD in order to design appropriate interventions. [3, Rank 4]

It is of equal or perhaps greater importance to accurately distinguish children with ASD from those with Global Developmental Delay (GLOBAL DEVELOPMENTAL DELAY) without ASD, who by definition present with delays in more than one developmental domain. This differentiation has strong implications for treatment recommendations and may also inform long-term prognosis. For example, current evidence supports intensive ASD-specific intervention services, such as Applied Behavior Analysis (ABA) therapy, for children with ASD to target social communication skills and challenging behaviors, but toddlers with GLOBAL DEVELOPMENTAL DELAY may instead show greater benefit from special education or rehabilitation services to bolster skills across broad developmental domains. Furthermore, individuals with cognitive delays without ASD present with heterogeneous functional outcomes, much like those with ASD. While some young children with GLOBAL DEVELOPMENTAL DELAY no longer show cognitive impairment as they get older, others show persistent deficits in intellectual functioning and are diagnosed with Intellectual Disability (ID), and still others present with emotional or behavioral issues (e.g., aggression). However, children with GLOBAL DEVELOPMENTAL DELAY are more likely to display symptoms associated with ASD than children with average cognitive abilities; therefore, cognitive impairment can present a particular obstacle to accurate diagnosis.

The differentiation between ASD

and GLOBAL DEVELOPMENTAL DELAY without ASD is most difficult in children with mental ages below 2 years; the number of signs differentiating the two disorders appears to increase both with age and developmental level. Cognitive level likely influences the emergence of clinical symptomatology, with children functioning at different intellectual levels potentially exhibiting distinct clinical features. It is therefore necessary to determine which specific symptoms can distinguish ASD from GLOBAL DEVELOPMENTAL DELAY in young children with significant intellectual impairment (i.e., low MA). [2, Rank 3]

Early Emergence of Autism Features

With increasing evidence in support of early intervention for ASD, there has been a push for earlier detection and diagnosis of very young children. It is important to consider the developmental prerequisites of behaviors that are impaired in ASD, as we do not expect to see these skills in children with mental or chronological ages lower than the age of emergence in typical development. ***Within the first year of life, typically developing infants show clear social-communicative behaviors (e.g., eye contact, responsiveness to their name, social smiling), whereas more advanced social behaviors (e.g., imitation, pretend play, pointing and following a point) may not appear consistently until the second year of life. Of note, repetitive behaviors are often seen in typically developing infants and toddlers and thus may not be useful indicators of ASD in early development.***

" Cognitive level likely influences the emergence of clinical symptomatology, with children functioning at different intellectual levels potentially exhibiting distinct clinical features "

Consistent with the typical developmental timetable of these behaviors, several features of ASD appear to emerge before 2 years, and even in the first year of life(as shown in fig.3). Infants with ASD show fewer facial expressions, specifically fewer directed toward other people, than their typically developing peers by 6 months. Parents report abnormal development of language precursors, including babbling and attentiveness to one's name. ***As early as 12 months, infants with ASD show less social engagement and play, as well as limited motor and vocal imitation. Between 6 and 18 months, children later diagnosed with ASD show less (or even***

declining) eye contact, social smiling, and social responsivity compared to their typically developing peers [4, Rank 5]

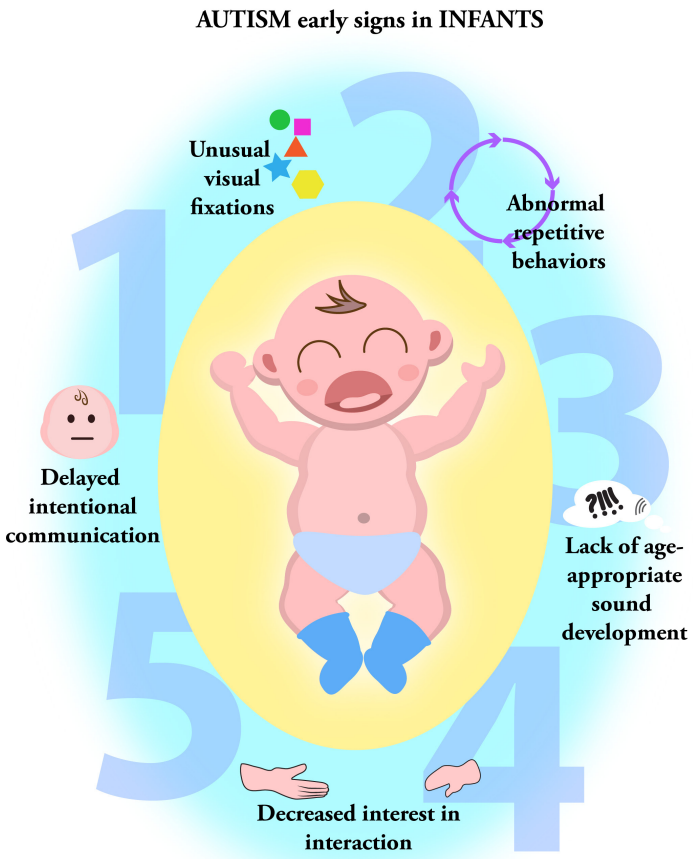

Figure 3: Infants and Autism

Behaviours Discriminating Autism and Global Developmental Delay

Consistent with the defining features of ASD, it has been suggested that deficits in social and pre-linguistic behaviors (e.g., response to one's name), reciprocal social engagement, and simple play are more indicative of ASD than delays in nonverbal problem solving, motor skills, and nonsocial adaptive behaviors, which are more associated with GLOBAL DEVELOPMENTAL DELAY. Given the finding that many children with intellectual impairment present with autism-like deficits, including atypical behaviors and attention problems, it is important to understand specific features that differentiate ASD and GLOBAL DEVELOPMENTAL DELAY in young children. Some researchers have suggested that children with ASD show deviations from the typical developmental course, whereas children with global cognitive deficits exhibit delays, although this finding is not universal.

Compared to children with purely cognitive delays, children with ASD tend to repeat sounds for non-communicative purposes and ignore bids for social interaction from adults and same-aged peers. They also exhibit less frequent vocal and gestural imitation and less sophisticated play than their intellectually impaired peers; that is, they may engage in sensorimotor, but not imaginative or cooperative, play. Of note, children with GLOBAL DEVELOPMENTAL DELAY, but not ASD, are more likely to respond to social bids and demonstrate early joint attention behaviors, including gaze monitoring, pointing, showing, and sharing, by 4 years. However, although stereotyped finger movements (e.g., wiggling and flicking) may be unique to children with ASD, both children with ASD and those with cognitive delays show hand

> **" Although stereotyped finger movements (e.g., wiggling and flicking) may be unique to children with ASD, both children with ASD and those with cognitive delays show hand flapping throughout the preschool "**

flapping throughout the preschool period. [6, Rank 4]

Discriminating ASD from intellectual impairment in the first year of life is especially difficult. ***Several studies compared children aged 9–12 months with ASD to those with equivalent developmental delays and to a group with typical development on ASD-related symptoms (i.e., early social communication, atypical motor mannerisms, etc.). Results showed that children with ASD were more likely to display abnormal affect, unusual posturing and mouthing, aversion to social touch, reduced orientation to visual stimuli, and poor responsiveness to name than those with GLOBAL DEVELOPMENTAL DELAY.***

This study was limited by a small sample size and reliance on children with known genetic disorders (e.g., Down syndrome) in the GLOBAL DEVELOPMENTAL DELAY group, but was consistent with results, which also found that 1-year-old infants with ASD demonstrated less social attention and responsiveness to their names than those with GLOBAL DEVELOPMENTAL DELAY. Both groups engaged in repetitive motor behaviors more frequently than typically developing peers. Taken together, these findings suggest that core social communication symptoms may be useful in identifying very young and cognitively delayed children with ASD, whereas atypical imitation, play, and motor movements may be seen in both ASD and GLOBAL DEVELOPMENTAL DELAY. [5, Rank 5]

Differential Diagnosis of Autism and Global Developmental Delay

The ability to differentiate ASD from other disorders, including GLOBAL DEVELOPMENTAL DELAY, is a key feature of a strong autism-specific diagnostic instrument, as accurate and timely diagnosis facilitates appropriate early intervention. Accordingly, it is important to evaluate the diagnostic utility of commonly used measures, particularly in very young and cognitively delayed children. ***The Autism Diagnostic Interview has long been considered a gold-standard tool for the diagnosis of ASD across the lifespan, but it is recommended for individuals with a mental age above 2 years.*** Below the age of 3 years,

diagnostic utility is mixed. Moreover, the ADI-R consistently over-diagnoses ASD in cognitively impaired and pre-verbal individuals, regardless of chronological age.

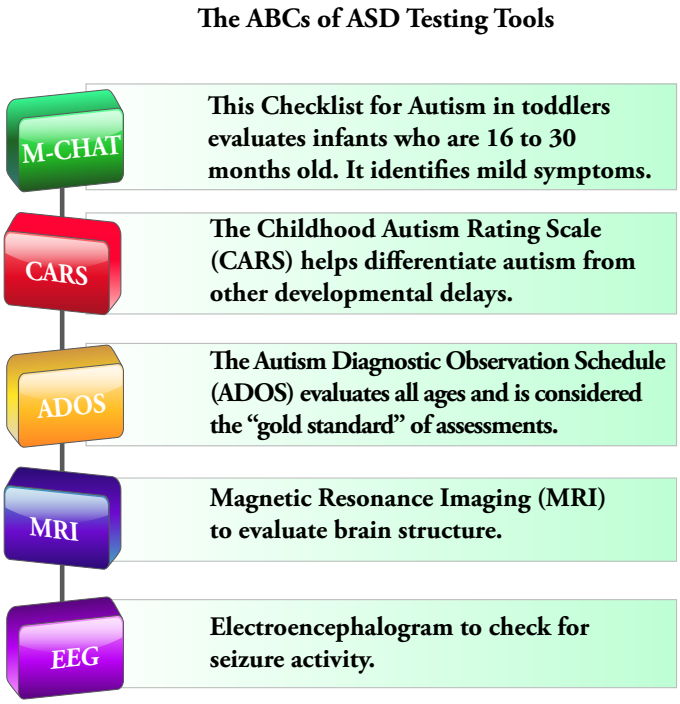

Figure 4: Testing tools for Autism Spectrum Disorder

The Autism Diagnostic Observation Schedule (ADOS) aims to evaluate the presence of autism symptoms using a structured play and interview session, with different modules designed for varying ages and language levels. The ADOS is recommended for use in children and adults with a mental age of at least 12 months.

One study found that the ADOS demonstrates high agreement with clinical judgment using DSM-IV-TR criteria in a sample of 16–31-month-old children, some of whom were functioning in the borderline to impaired ranges on standardized developmental testing. However, other researchers have shown that the ADOS tends to over-classify cognitively impaired children over the age of 3 years, with particularly poor ability to discriminate ASD from other disorders in mental ages at or below a 15-month level. It has been suggested that the expectations for interaction in the ADOS are too high for cognitively delayed children. A newer Toddler Module of the ADOS was developed to address some of these concerns, although it continues to be less valid when used with toddlers who are functioning at or below a 15-month level and not walking independently. [8, Rank 4]

An observational research measure, the Autism Observation Scale for Infants (AOSI), was specifically designed to detect signs of ASD in children between the ages of 6 and 18 months. Elevated scores on the AOSI by 1 year of age are predictive of social communication symptoms at age 24 months and a diagnosis of ASD at age 3 years. However, despite its potential utility for the very early diagnosis of ASD, the AOSI remains an unpublished research instrument.

The Childhood Autism Rating Scale (CARS) combines information from caregiver report and direct observation in a clinician-completed rating scale. Although used with individuals of all ages, the meas-

ure is recommended for those over age 2 years. In toddlers with varying mental ages and older children with intellectual impairment, the CARS shows high agreement with clinical judgment and good sensitivity in diagnosing ASD. It is possible that, because it incorporates subjective clinical judgment, the CARS is more consistent with clinical best estimate of ASD, particularly in very young and cognitively impaired individuals. [7, Rank 3]

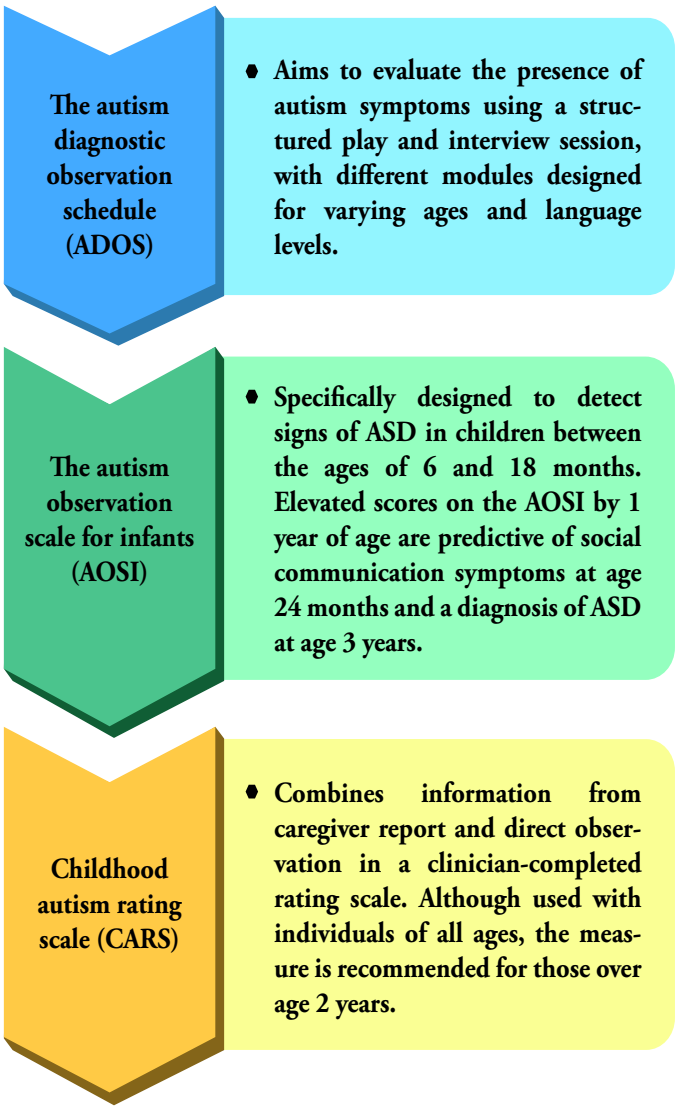

Figure 5: Most common Autism Diagnostic Interview tools

The Impact of Developmental Level on the Presentation of Autism Symptoms

Both the ADOS and CARS demonstrated approximately 80% agreement with clinical best estimate diagnosis of ASD in children with low MA. Specifically, the ADOS agreed with clinical judgment in 79.2% of cases, whereas the CARS agreed with clinical best estimate in 83.3% of cases. In cases of disagreement, the ADOS consistently over-classified children with low MA as having ASD, but CARS classifications were distributed between over- and under-classifying these children.

Symptom profile analyses suggested that children with GLOBAL DEVELOPMENTAL DELAY show minimal signs of ASD, with the exception of mild deficits in more advanced behaviors (e.g., pointing and pretend play). ASD-low MA participants were more severely impaired than children with ASD-higher MA on most autism symptoms. In particular, social-communicative skills that typically appear toward the end of the first year of life or into the second year, such as pointing, integrating gaze, sharing enjoyment with others, requesting, giving, initiating and responding to joint attention, making social overtures, and pretend play, differentiated children with ASD-low MA from those with ASD-higher MA.

However, certain core social behaviors that are typically seen early in development (i.e., in the first year of life), specifically eye contact, social smiling, directing facial expressions toward others, and responding to one's name, did not differ between these two groups, nor did the ASD groups differ on atypical sensorimotor behaviors (e.g., unusual sensory interests, hand and finger mannerisms, and repetitive interests or stereotyped behaviors). [9, Rank 3]

Diagnosis of Autism in Children with Low Mental Age

Despite the recent push to identify ASD earlier, perhaps within the first year of life, no commercially available diagnostic tools are recommended for use in children under 12 months. The diagnostic utility of two widely used measures, the ADOS and CARS, was explored in a well-defined subgroup of toddlers with cognitive functioning below a 12-month age equivalence; in fact, these children were functioning at a 9-month-old level, on average, across both verbal and nonverbal cognitive domains.

Results suggested that the ADOS, although significantly aligned with clinical judgment in most cases, tended to over-classify a large minority of children with low MA as having ASD when they received a clinical diagnosis of GLOBAL DEVELOPMENTAL DELAY. In the context of developing improved ADOS diagnostic algorithms, it was indicated that the task demands of the ADOS may be too challenging for lower-functioning children. All toddlers in the sample were administered medications, which are intended for pre-verbal children and those with single words. In addition to simple to-and-fro activities, such as bubble play and interaction games (e.g., peekaboo), they asks toddlers to both initiate and respond to joint attention by social referencing, as well as to engage in functional and symbolic imitation and creative pretend play (e.g., acting out a birthday party scenario, which may be unfamiliar for very young or cognitively delayed children). [10, Rank 2]

Autism as a Life-long Neurodevelopmental Condition

Autism is a life-long neurodevelopmental condition interfering with the person's ability to communicate and relate to others. Since the earliest epidemiological surveys, a wealth of data has become available, indicating a much higher prevalence of the condition than previously thought. It is now recognized that some individuals with the condition are able to lead independent and fulfilling lives, whereas for others the impact can be severe, interfering significantly with quality of life. While the global

burden of autism is currently unknown, in the United States and in the UK, the annual societal cost of the condition exceeds several billions.

Increased recognition, understanding, and awareness of autism in the last few decades have been, in part, driven by the significant growth in research evidence. While many aspects of autism remain poorly understood, major advances have been made in terms of highlighting the genetic, biological, environmental, and developmental origins of the condition. Large-scale and well controlled cohort studies following-up pregnant mothers are likely to clarify the effects of some pre- and perinatal risk factors implicated in autism. Significant strides have also contributed towards developing and validating screening and diagnostic instruments, helping to reduce heterogeneity in clinical characterization in research studies.

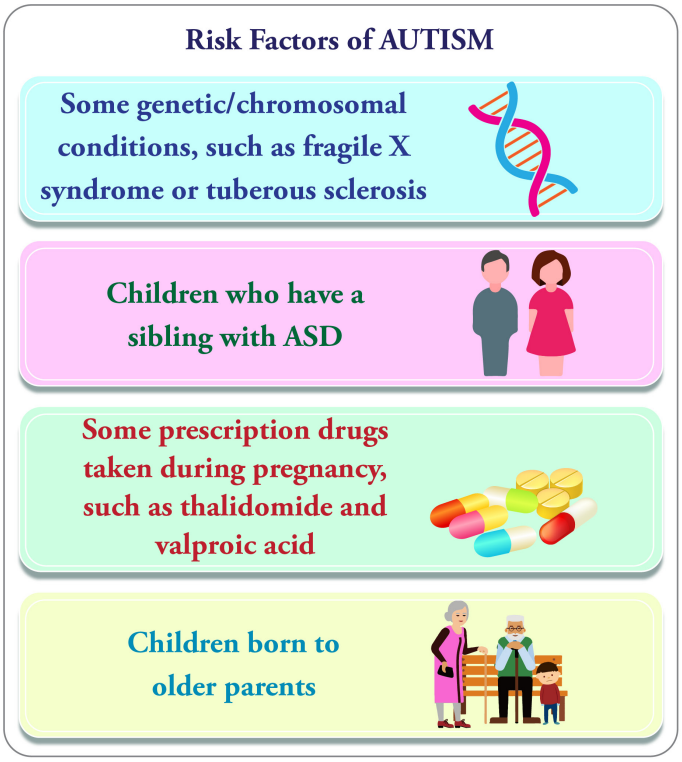

Figure 6: Risk factors of Autism Spectrum Disorder

While some of these diagnostic tools remain highly resource intensive, they are increasingly used in clinical settings, as they provide rich and systematic information to inform service provisions where those are available. However, even in high-income countries, provisions for screening, diagnosis, and intervention are highly variable and many cases absent in community settings. [11, Rank 5]

Bridging the Global Gap between Evidence and Practice In Autism

Advances in autism research have contributed towards bridging the gap between evidence and practice in some countries, but there is little systematic information available with regards to the impact of the condition on most of the world's population. Frequently regarded as essential for advancing basic research and strategic for informing policy and developing services, epidemiological studies have emerged as a clear priority within several global initiatives. The charity Autism Speaks in partnership with the US Center for Disease Control (CDC) launched the

International Autism Epidemiology Network, bringing together researchers worldwide and focusing specifically on service improvements in developing countries. According to the network, prevalence studies for pervasive developmental disorder (PDD) are ongoing in Australia, Mexico, Finland, Portugal, Iceland, India, Vietnam, Taiwan, South Africa, and Uganda.

Focusing on a broader context than autism, the Movement for Global Mental Health has identified a clear treatment gap, particularly pronounced in low- and middle-income countries. Epidemiological data on the burden of mental and neurological disorders and systematic mapping of relevant services in low- and middle-income countries encouraged World Health Organization (WHO) to launch the mental health Gap Action Programme (MHGAP). Moreover, the Global Alliance for Chronic Disease, which groups several agencies including Australia's National Health Medical Research Council, the Canadian Institutes of Health Research, the Chinese Academy of Medical Science, the UK's Medical Research Council, and the United States' National Institutes of Health, announced a program to identify the world's "Grand Challenges in Global Mental Health".

The reasons for why epidemiological surveys are viewed as a priority extend beyond the need for objective and robust estimates of prevalence. These provide additional valuable benefits as they often result in systematic information regarding existing services and may help in assessing the needs and priorities for each community. In the long run, the availability of comparable estimates from different geographic regions may also enable testing challenging hypotheses regarding the etiology of PDD. [11, Rank 5]

Recent Global Prevalence Estimates of Autism

Available studies from Northern European countries (UK, Iceland, Denmark, Sweden) provide estimates for combined PDD as well as AD. Much less data are available from other European countries, namely from France, Germany, Portugal, and Israel. Sample sizes of multiple surveys estimating AD varied from 826 to 490 000 participants, with an age range of birth to adulthood. Prevalence rates varied from 1.9/10 000 to 72.6/10 000 with a median value of 10.0/10 000. In studies published since 1999, the median rate was 18.75/10 000. Studies providing estimate for combined PDD ranged in sample size from 2536 to 134 661 participants. All these surveys were published since 2000, and the majority since 2006. The diagnostic criteria reflect reliance on modern diagnostic

schemes. There was high variation in prevalence proportions that ranged from a low 30.0/10 000 to a high of 116.1/10 000, with a median rate of 61.9/10 000.

The wide range of prevalence estimates reported in these studies may be attributed, at least in part, to methodological issues outlined earlier. Furthermore, such estimates should always be regarded in the context of the imperfect sensitivity of case ascertainment that results in downward biases in prevalence proportions. For example, in the Danish investigation, case finding depended upon notification to a National Registry, a method that is usually associated with lower sensitivity for case finding. By contrast, case-finding techniques used in other surveys relied on multiple and repeated screening phases, involving both different informants at each phase and surveying the same cohorts at different ages, which certainly maximized the sensitivity of case identification. [12, Rank 1]

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Clinical Presentation of Autism in Various Countries

America

The sample sizes of studies estimating AD in America were fairly large. Despite huge variation in ranges, both AD and PDD median estimates correspond closely to those derived from Northern Europe. Similar to the latter studies, a likely underestimation of the true population rates holds in this region as well. For example, the Atlanta survey by the CDC was based on a very large population and included younger age groups than subsequent CDC surveys, and age specific rates were in fact in the same range in some birth cohorts.

Less data were available from other countries in America. Two published studies from Argentina and Venezuela along with unpublished reports from Brazil and Mexico provided prevalence data. There was also one study from the Caribbean (Aruba). All of the studies had relatively small sample sizes. The two studies from Venezuela and Aruba provided similar AD estimates.

With the exception of one study conducted, the remaining estimates of administrative prevalence was available from Mexico through a registry of minors with

disabilities reporting the number of children identified with autism, combined with Mexican census figures. Based on these figures the rate for childhood autism in Mexico was estimated to be 14.3 per 10 000. The estimates in those studies are smaller than those reviewed earlier but it is difficult to compare the findings given the limited data and methodological differences among studies. [16, Rank 3]

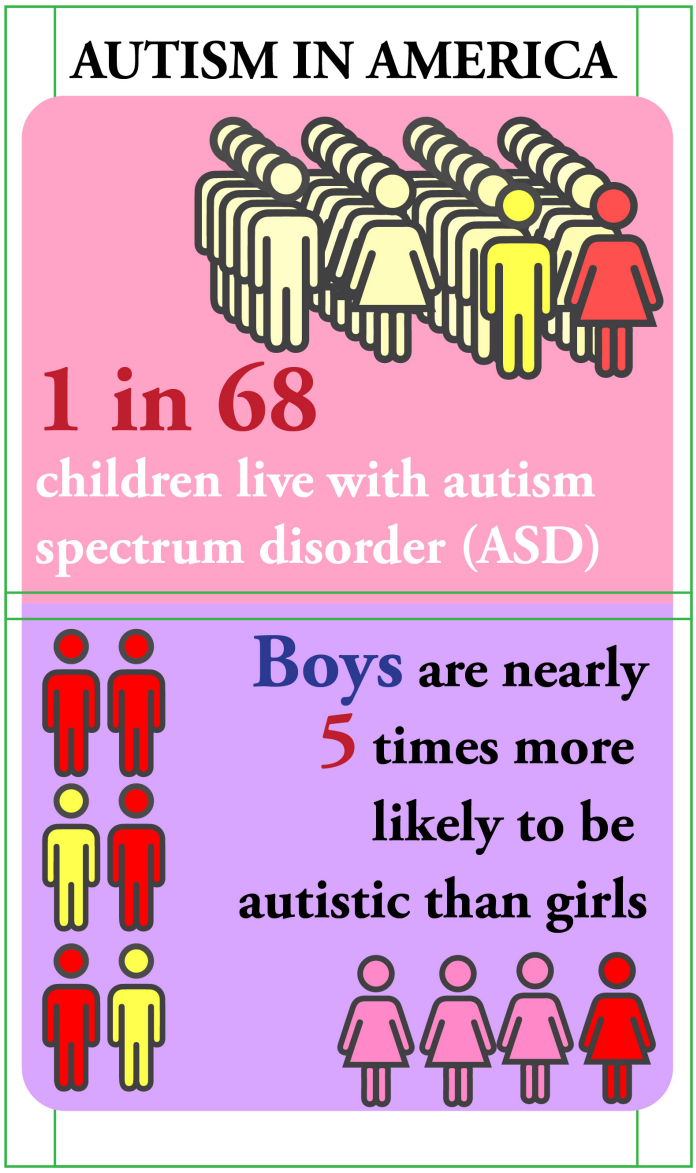

Figure 7: Epidemiological data of Autism Spectrum Disorder in America

Europe

Clinical characterization in Europe has increasingly relied on standardized measures, serving to reduce heterogeneity in clinical judgment. Assessments in several of the studies were often performed with these diagnostic measures that match the more dimensional approach for case definition. Extensive discussion of clinical presentation has been previously presented based on these studies. To summarize, males consistently outnumbered females in the vast majority of studies, with a ratio ranging from 1.33 to 16.0 for AD and 3.3 to 15.7 for PDD. In studies where IQ scores were available, the proportion of participants with normal IQ was 15.6–86.7% for AD and 45–85.3% for PDD.

A few studies provided information on the social class of the families of autistic children. Of these, two older studies suggested an association between autism and social class or parental education. Studies conducted thereafter provided no evidence for the association. Thus, the epidemiological results suggest that the earlier findings were probably due to artifacts in the availability of services and in the case-finding methods, as already shown in other samples.

Some investigators have mentioned the possibility that rates of autism might be higher among immigrants in Northern

Europe. A meta analysis including five studies found weak (nonsignificant) association between autism and mother's birthplace. Serious methodological caveats related to these comparisons have been extensively discussed, including small samples, variation in rate of immigration in the areas samples, and the lack of a reasoned biologically plausible hypothesis linking immigration to autism. [13, Rank 2]

Western Pacific

While detailed medical conditions and ASD phenotype data were not available, several studies reported similarities in the PDD phenotypes within this region. Excluding older studies from Japan, AD and PDD were more prevalent in boys than girls in the epidemiological studies. In Japan, 66.4% of participants in the study with the highest prevalence estimate had IQ scores within the normal range. By contrast, all cases with AD identified in the population-based prevalence study in China had intellectual disabilities. One study speculated that autistic children with average cognitive function or mild intellectual disabilities might be neglected during the screening and case-ascertainment process. Another study reported that the AD prevalence was higher among urban children than children in suburban area. Authors also noted that parents in urban areas had higher education and higher family income, leading to better accessibility for clinical care and rehabilitation services in these families. [14, Rank 2]

Southeast Asia

A few studies characterized relatively small samples of children in tertiary care settings in India among a larger literature on intellectual disabilities from the region. The studies had a high but variable male-to-female ratios. Across studies, the concern that most commonly led to referral from medical professionals was language delay or regression in language skills, followed by social difficulties and hyperactivity. Most children received the diagnosis of ASD between 3 and 6 years. The time between recognition of symptoms by caregivers and diagnosis averaged about 2 years. Three Indian studies noted that the majority of families were from middle-class backgrounds and postulated that the higher

> **“ The biochemical basis suggests that several brain neurotransmitters, e.g., dopamine (DA), serotonin (5-HT), gamma-amino butyric acid (GABA), acetylcholine (ach), glutamate (GLU) and histamine (HA) participate in the onset and progression of ASD. ”**

socioeconomic families do not attend state-run facilities while the lower socioeconomic groups may not access care unless the child is acutely ill. Regression of skills was found in 25% of the children in one study. Seizures were associated with ASD in 6.8–31% of children. Intellectual disability was the most common co-morbid condition ranging from 24 to 95% of children. Perinatal events were examined in three studies; two reported such events in up to 25% of the children whereas the third found no significant perinatal events. [15, Rank 3]

Eastern Mediterranean

Similar to other regions, a number of studies report a high but variable male-to-female ratios. The gender ratio in the Iranian study was more equally distributed between males and females, but the rate reported in a study most likely reflects that of PDD symptoms among school-aged children rather than estimates of the disorder because a stage of diagnostic confirmation was not conducted. One study from Saudi Arabia reported that girls were older than boys in a tertiary referral center

Global Variation in Prevalence Estimates of Autism

Epidemiological surveys of autism and AD and PDD have now been conducted in several countries. Methodological differences in case definition and case-finding procedures make between survey comparisons difficult to perform. However, most studies conducted in different geographical regions and by different teams converge to estimates to similar results for AD and for all PDDs combined. This is currently the best estimate for the prevalence of PDDs available. The estimate represents an average figure and there is substantial variability across studies. [17, Rank 1]

Etiology of Autistic Spectrum Disorder (ASD)

ASD is broadly considered to be a multi-factorial disorder that results from genetic as well as non-genetic risk factors. There is cumulative evidence for the involvement of genetic factors in the etiology of ASD, since siblings born in families with ASD are at 35–40% greater risk to develop ASD and with an increase in the current rate of approximately 1% from a rate of 0.05%. Moreover, genetic studies revealed that alteration in the developmental pathways of neuronal and axonal structures that are strongly involved in synaptogenesis emerge from single gene mutations. It is likely that ***interactions between multiple genes, and variability in expression as a result of epigenetic factors and exposure to environmental factors are responsible for ASD.***

In a clinical study involving a twin, it was appraised that the risk of developing ASD was 35–40% due to genetic variability, and the remaining 60% was contributed to by prenatal, perinatal, and postnatal environmental factors. Accordingly, environmental factors implicated with ASD included prenatal and perinatal complications, birth and neonatal complications, viral infection, autoimmune diseases, and exposure to teratogens and maternal anticonvulsants such as valproic acid (VPA). Therefore, an increased understanding of the interface between genetic and environmental factors in the pathogenesis of ASD may lead to an optimized therapeutic strategy. [19, Rank 5]

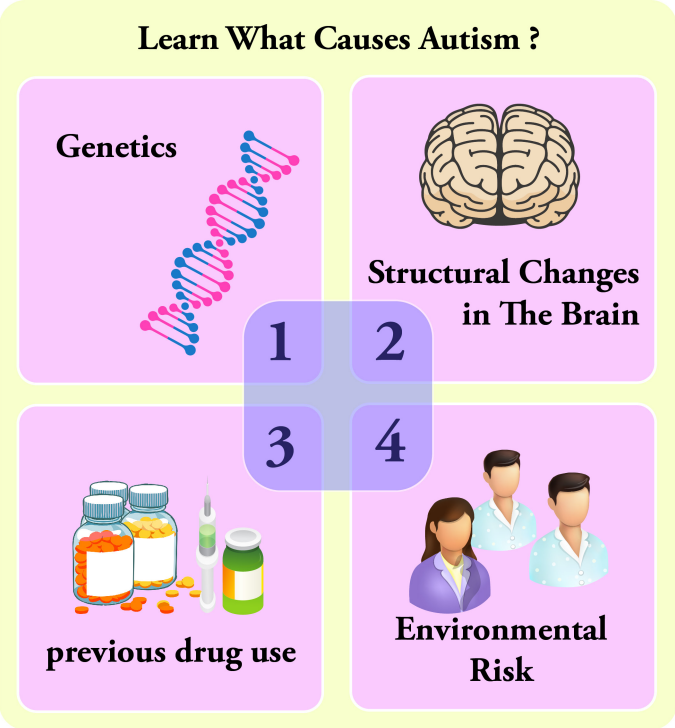

Figure 8: Causes of Autism Spectrum Disorder

Correlation of Neurotransmitters Dysfunction to Autism

Research has also focused on the study of neurotransmitters, in search of sensitive and specific markers of ASD as well as potential therapeutic interventions. The role of several central neurotransmitters (e.g., 5-HT, ACh, DA, GABA and Glu) in initial brain development may substantiate to be a significant area in studying the etiology of ASD. Certain disruption of brain neurotransmissions early during the development phase of the CNS may demonstrate early pharmacological intervention that helps to cure and maybe even preclude some of the severe behavioral symptoms of ASD. Ideally, the work in genetics may be able to explain these neurochemical defects at birth, providing possible appropriate medical treatment for infants who are at increased risk for ASD. This would completely exhibit new therapeutic tactic to the clinical control of ASD

Serotonin

Among all neurotransmitters investigated so far in ASD, Serotonin has motivated the most research efforts and investigations. Serotonin signaling facilitates several neural processes including neurogenesis, cell migration and survival,

synaptogenesis, and synaptic plasticity. Interestingly, high Serotonin levels in the blood have been described for up to 45% of tested ASD subjects. Moreover, preclinical investigations using ASD-like animal models reported that hyperserotonemia significantly reduced the motivation for social interest through inhibition of separation distress, potentially accounting for the social impairments found in ASD individuals. Furthermore, Serotonin was found to accumulate mainly in platelets utilizing the specific 5-HT transporter. [20, Rank 2]

Dopamine

Dopamine (DA) plays a fundamental role in brain functioning, and the pathophysiological role of dopaminergic system (DS) deficits in ASD is well recognized, with the wide clinical use of antipsychotics that mainly target the D2 receptors. Interestingly, in a preclinical study, it has been shown that those with increased dopaminergic neurotransmission in the dorsal striatum via the suppression of dopamine transporter expression in substantia nigra neurons or the optogenetic stimulation of the nigro-striatal circuitry exhibited significant deficits in sociability and repetitive behaviors relevant to ASD pathology in several models, while these behavioral changes were blocked by using D1R antagonists.

GABA and Glutamate

Gabaminergic as well as glutaminergic systems are also proposed as potential mechanisms for ASD. Consequently, mutations in the respective synaptic proteins would lead to defective neurotransmissions at excitatory and inhibitory synapses, leading to disruption of excitatory-inhibitory balance of neurotransmissions in postsynaptic neurons, a key mechanism which has strongly been associated with ASD. [20, Rank 2]

Current Pharmacological Interventions for Autism

Based on the aforementioned abnormalities in genes as well as various neurotransmitter systems, studying the effects of a given drug on core symptoms in ASD is very challenging. Despite advances in early diagnosis and intervention, efficacious reversal of core autistic symptoms is still not accomplished to date. At present time there is no definite pharmacological treatment for ASD but treatments for ASD are based on behavioral therapies and the use of highly controlled learning environments. The recent approaches to treatment of ASD set behavioral therapy and atypical language development, as keystone for ASD therapy along with other treatments that tends to ameliorate associated symptoms

and not the core deficits. The heterogeneity of clinical and behavioral features in children diagnosed with ASD contributes to the difficulty in understanding the pathophysiology of this disorder, and consequently, no specific treatment can be effective for all ASD children. Therefore, subgrouping of children based on responses to intervention is essential. As mentioned above, targeting ASD core symptoms for complete and effective treatment has been challenging and not yet achieved, however ***several pharmacological medications maybe effective in various associated symptoms that often cause significant impairments in ASD. These associated symptoms of ASD include inattention, hyperactivity, anxiety, sleep disturbances, irritability, repetitive behavior, aggression and self-injury.***

Antipsychotics are often used for therapeutic management of ASD symptoms in children. Currently, atypical antipsychotics risperidone and aripiprazole are the only two drugs which have so far been approved by FDA for improving behavioral symptoms associated with ASD, however, there are several other pharmacological interventions that show effective clinical management of ASD symptoms. Accordingly, therapeutic benefits have been observed and described with several classes of drugs including selective serotonin reuptake inhibitors (sertraline, citalopram, fluoxetine) for anxiety and repetitive behaviors, psychostimulant (methylphenidate) for hyperactivity, opioid antagonist (naltrexone) for hyperactivity, and atypical antipsychotics (risperidone, olanzapine, clozapine) for temper tantrums, aggression, or self-injurious behaviour. [21, Rank 3]

Atypical Antipsychotics

Clozapine belongs to the class of atypical antipsychotic medication mainly used for schizophrenia that does not improve following the use of other antipsychotic medications. In patients with schizophrenia and schizoaffective disorder it may decrease the rate of suicidal behavior. It is possibly more effective than typical antipsychotics and in patients who are resistant to other medications. Clozapine was found to improve hyperactivity and aggression in ASD children, adolescents and adults, but has a limited clinical use because of it's hematological safety profile a potential of lowering the seizure threshold in epilepsy patients, necessitating monitoring procedures of patients taking this medication.

The antipsychotic medication with risperidone is mainly approached in ASD patients with SCH, bipolar disorder, and/or irritability symptoms, as this drug has revealed to be better than placebo in

treating irritability, repetitive behavior, aggression, anxiety, depression and nervousness. Moreover, risperidone has shown a neuroprotective effect and has enhanced the antioxidant and neuroprotective activity of astroglial cells in brain disorders such as ASD without clinical evidence of extrapyramidal side effects or seizures except mild sedative effects.

However, other side effects with use of risperidone were reported to include increased appetite, fatigue, dizziness and drowsiness. Aripiprazole is another atypical antipsychotic primarily recommended for the treatment of SCH and bipolar disorder. Other uses include an add-on treatment for major depressive disorder, tic disorders, and irritability associated with ASD, as it shows a different mechanism of action from those of the other atypical antipsychotics (e.g., clozapine, and risperidone). [22, Rank 5]

Neurotransmitter Reuptake Inhibitors

The class of neurotransmitter reuptake inhibitors, e.g., fluoxetine (selective serotonin reuptake inhibitor, SSRI) has shown numerous prospective therapeutic benefits, including decreases in rituals, stereotyped and repetitive monotonous behaviors in ASD children and adolescents. Fluoxetine belongs to the class of SSRI which does not significantly inhibit norepinephrine and dopamine reuptake at therapeutic doses. Fluoxetine was found to produce some adverse effects including disinhibition, hypomania, agitation, and hyperactivity.

> **“ Cognitive functioning is an important predictor of response to intervention and functional outcomes in individuals with ASD. ”**

Fluvoxamine is a drug which functions as a SSRI and σ1 receptor agonist. Fluvoxamine is used mainly for the treatment of obsessive-compulsive disorder, and is also used to treat major depressive disorder and anxiety disorders such as panic disorder and post-traumatic stress disorder. Notably, fluvoxamine is approved to treat social anxiety disorder. Fluvoxamine has also shown similar potential effects as fluoxetine against ASD. In a clinical trial, fluvoxamine was found to be well tolerated in ASD adults and it has improved compulsive as well as repetitive behaviors and aggression. Other SSRIs, including sertraline, paroxetine and escitalopram, showed almost the same potential benefits and adverse effects as compared to fluoxetine and fluvoxamine. Venlafaxine is another SSRI which has, also, shown improve-

ments of restricted behaviors, decreased interests, social deficits, hyperactivity and communication problems in individuals with ASD [21, Rank 3]

Tricyclic Antidepressants

The second-generation tricyclic antidepressant nortriptyline is used in the therapeutic management of major depression and childhood nocturnal enuresis (bedwetting), chronic fatigue syndrome, chronic pain and migraine, and labile affect in some neurological brain disorders. Clomipramine is another tricyclic antidepressant used for the treatment of obsessive compulsive disorder, panic disorder, major depressive disorder, and chronic pain. Interestingly, nortriptyline has been described to be effective in children with ASD as it improved the hyperactivity, aggressiveness, and ritualized behavior, while imipramine was not well tolerated in ASD children. In a clinical trial, 58% of ASD subjects have found clomipramine to be superior to placebo and the antidepressant desipramine in improving ASD symptoms, anger, and compulsive and ritualized behaviors. In another clinical study, clomipramine has caused several adverse effects such as sedation and worsening of behaviors like aggression, irritability, and hyperactivity. [22, Rank 2]

> **" ASD can be difficult to diagnose in very young children, as many of the defining characteristics (e.g., peer- peer relationships, lack of conversation skills, and restricted or stereotyped interests) are age-or development-specific. "**

Anticonvulsants

Lamotrigine, a member of the sodium channel blocking class of anticonvulsants clinically used in the treatment of children diagnosed with epilepsy, decreased symptoms in approximately 62% of the ASD individuals, and no considerable change among placebo-treated and lamotrigine-treated patients was observed in a study comprising 35 patients diagnosed with ASD. On the contrary, Valproic acid (VPA) with its anticonvulsant effect recognized based on its blockade of voltage-dependent sodium channels and increased GABA levels in the brain has shown -as an orphan drug-valuable effects in improving various symptoms and psychiatric comorbidities, e.g., receptive language, affective instability, and aggression, without appreciable clinical effects on core symptoms of ASD.

Notably, VPA has been reported to be an inhibitor for histone deacetylase (HDAC), an enzyme which plays –together

with other HDACs- an essential regulating role in gene transcription and phenotypic differentiation. Accordingly, numerous studies reported that specific expression forms of HDAC1 and HDAC2, which are categorized as class I of HDACs, in the murine brain are existent at various developmental ages with HDAC1 expressed in neural stem cells/progenitors and glia, and HDAC2 being upregulated in postmitotic neuroblasts and various but not in fully differentiated glia. These clinical observations for several antiepileptic drugs demonstrate that the prevalence of psychopharmacotherapy and polypharmacy in ASD patients is considerable, which is probably due to the treatment of non-core ASD symptoms and psychiatric comorbidities, despite a lack of pharmacological treatment options for ASD core symptoms. [23, Rank 3]

Glutamate Antagonist

Levels of glutamate have been found to be excessively increased in post-mortem brain samples of some ASD individuals. Numerous studies have publicized the effectiveness of several glutamate antagonists, e.g., amantadine and memantine, in ASD patients. In a controlled clinical trial, amantadine showed improving effects on hyperactive behavior and inappropriate speech in ASD children. Also, the clinical use of memantine in the treatment of ASD individuals has shown therapeutic progresses in regard to memory, hyperactivity, irritability, language, social behavior and self-stimulatory behavior

Anticholinesterase Inhibitors

Dysfunction of brain cholinergic neurotransmission has been described in several patients diagnosed with ASD. Therefore, acetylcholinesterase inhibitors, e.g., rivastigmine, donepezil, and galantamine, have in many studies been investigated for the use in ASD children. Interestingly, the clinical application of rivastigmine in ASD children significantly relieved overall ASD behaviors, however, several adverse effects including nausea, diarrhea, hyperactivity and irritability were reported.

Among acetylcholinesterase inhibitors, donepezil has shown capability to improve irritability and hyperactivity of ASD children. Moreover, galantamine produced substantial improvements in hyperactivity, irritability, social withdrawal, inappropriate speech, attention deficiency, and reduction in anger in children diagnosed with ASD. These improvements observed for several acetylcholine esterase inhibitors strongly support the hypothesis that enhancing the cholinergic neurotransmission in ASD results in positive therapeutic effects. [24, Rank 4]

Psychostimulants

Methylphenidate, the most commonly known CNS stimulant widely used in the therapeutic management of attention deficit hyperactivity disorder (ADHD) and narcolepsy, is commonly indicated for ASD children and adolescents. Methylphenidate mainly acts as a norepinephrine-dopamine reuptake inhibitor (NDRI). In numerous controlled studies, methylphenidate palliated several behavioral ASD features including impulsivity, attention deficiency, and hyperactivity, but it correspondingly exhibited some initial adverse effects such as aggression, anorexia, and increased wakefulness (insomnia)

Adrenergic Receptor Agonists

Oral or transdermal administration of selective centrally acting adrenergic agonist, e.g., clonidine, have revealed to improve mood instability, hyperactive behavior, aggressiveness and nervousness in ASD individuals. Clonidine is a drug used to treat high blood pressure, ADHD, anxiety disorders, tic disorders, withdrawal (from either alcohol, opioids, or smoking), migraine, and certain pain conditions, with largely tolerable adverse effects.

Also, previous clinical trials carried out with clonidine in ASD subjects delivered evidences for the clinical effectiveness and safety profile in ASD and related brain disorders. Moreover, a retrospective study revealed that the use of guanfacine, a selective adrenergic receptor agonist used in the treatment of ADHD, anxiety, and hypertension, was accompanied with enhancements in insomnia, attention deficiency, hyperactivity, and tics. However, the most common adverse effects observed with guanfacine were mood alteration fatigue, blurred vision, and headache. [25, Rank 1]

Opiate Antagonists

Based on the reputed role of endogenous opioids such as β-endorphin and encephalin in the regulation of social behavior, the opiate antagonist naltrexone has been assessed in ASD. The results observed in numerous studies for naltrexone showed that it might be able to treat behavioral aberrations perceived in ASD patients and induced by dysfunction of the brain opioid system. Moreover, numerous studies revealed the significant improvements of various behavioral symptoms obtained with the use of naltrexone in ASD children. Furthermore, these studies reported that naltrexone treatment provided substantial enhancements in self-injurious behavior, hyperactivity, social withdrawal, agitation and irritability in ASD patients. [26, Rank 2]

> " Intensive ASD-specific intervention services, such as Applied Behavior Analysis (ABA) therapy, for children with ASD to target social communication skills and challenging behaviors, "

The aforementioned described drugs act on different targets to therapeutically manage the behavioral as well as psychiatric symptoms of ASD. However, several brain regions are altered in ASD individuals, resulting in loss of neuronal function, and behavioral and sensory impairments, including inattention, hyperactivity, mood fluctuations, aggressiveness, agitation, social deficits and repetitive and restricted behavior. In the brain, the plasticity of brain tissue, nerve tangling and imbalanced production of several neurotransmitters are all implicated on evolution in ASD individuals. Apart from environmental factors, other pathological conditions such as immunological problems, chronic neuroinflammation, oxidative stress, mitochondrial dysfunction are involved in etiopathogenesis of ASD.

Up until now, there is no approved drug existing in the market which is specific for treating symptoms associated with ASD, however, preclinical and clinical research and development are in progress to find new therapeutic entities. Currently, there are several candidates that successfully passed different clinical phases of drug development, with different pharmacological targets to palliate ASD behavioral and neurological symptoms [27, Rank 3]

Sex Differences in the Manisfestation of Austistic Traits

Sex differences in the manifestation of autistic traits have been investigated in a range of studies over the past few decades. Early work in this field generally found that autistic females were more severely impaired than their male counterparts, presenting with lower IQs and more prominent autistic traits. Subsequent studies have found that overall, particularly after controlling for IQ, there are not significant differences by sex in the degree of social-communication impairment, but that restricted/repetitive behaviors (RRBs) are more prominent in males. However, important sex differences have been identified in the ways in which socio-communicative impairments manifest, particularly among those without co-occurring intellectual disability (ID).

Autistic females without ID tend to show more developmentally appropriate

vocabulary and core language skills than their male counterparts, though not always. Given that language delays are the most commonly reported first concern among parents of children with ASD, this difference may have important implications for diagnostic timing and accuracy. Autistic females without ID are also more likely to have intact play and imitation skills, which are often considered core impairments in ASD.

Additionally, in contrast to the social isolation classically described among autistic boys, girls are more likely to be described as "clingy" or overly concerned with being liked by peers. Furthermore, some studies have found that parents rate females as being more socially impaired than their male counterparts, even when differences are not apparent on performance-based measures of social-communication skills. Additionally, some authors have noted that sex differences in RRBs may also be driven by clinician bias, as females may have restricted interests in more "normative" content areas (e.g., books, celebrities, animals). It is also worth noting that prior studies describe patterns of sex differences among males and females identified by currently available measures. [28, Rank 5]

> **" Risperidone and aripiprazole are the only two drugs available clinically for improving behavioral symptoms of ASD, approved by Food and Drug Administration (FDA). "**

Autism spectrum disorder (ASD) is identified in females at a substantially lower rate than in males, with most epidemiological studies reporting approximately a 4:1 male to female ratio. However, a recent meta-analysis of epidemiological studies found that the true ratio is likely closer to 3:1, with findings suggesting that autistic females1 are more likely to be missed. These studies and others have hypothesized that autistic traits may be "camouflaged"2 in females and that current diagnostic procedures may be biased against females. This contrasts strongly to the longstanding belief that females are simply at reduced risk for developing ASD, based on the consistent finding of lower prevalence rates among females.

Studies exploring the etiological basis of ASD have found some support for the observed sex differences in diagnostic rates. Many in the field have described a female protective effect, by which female sex in some way directly reduces the risk of ASD. For instance, there is a higher rate of ASD recurrence in families of female probands than in those of male probands, as well as higher rates of autistic traits in the families of female probands.

There are also reports that autistic females carry a higher mutational burden, including a higher frequency of both copy number variants (CNVs) and single-nucleotide variants (SNVs). These findings suggest that there may be a higher genetic threshold for ASD in females relative to males. Hormonal effects have also been hypothesized to play a role in the etiology of ASD and in the observed sex differences in prevalence. Elevated levels of fetal testosterone have been implicated in the development of ASD, and there have been some findings of higher levels of testosterone in autistic females as compared to typically developing females. [29, Rank 4]

Movement Abnormalities in Autism

Autism spectrum disorder (autism) is a developmental disorder characterized by impaired communication and social interaction, and restricted and repetitive interests. Movement atypicalities have been linked with autism in motor abnormalities such as 'sluggish' reflexes, 'clumsy' gait and an absence, from an early age, of anticipatory postures when being picked up.

Several studies have noted that autistic participants are generally less stable in their posture and typically exhibit a tendency to put most of their weight on one heel/-toe. Similar patterns have been observed in subsequent studies of postural sway; for instance, autistic children demonstrate abnormalities when standing and looking straight ahead, standing while dual-tasking, standing with eyes closed, standing on unstable surfaces and standing on a sway-referenced platform.

> **"Infants with ASD show fewer facial expressions, specifically fewer directed toward other people, than their typically developing peers by 6 months."**

In one study it was found that compared with typical individuals, autistic children (6–14 years) exhibited trunk postural abnormalities, difficulties in walking in a straight line, a marked loss of smoothness (an increase in the jerkiness of movement) and, in general, a stiffer gait in which the usual fluidity of walking was lost. In a comprehensive review of gait atypicalities in autistic children, it was found that the most commonly reported atypicalities concerned step width, step and stride length, reduced velocity and increased time in the stance phase of gait. On the basis that increased step width provides a wider base of support, and reduced velocity and step and stride lengths help a walker to keep their centre of gravity within this base of support, they

argue that together these results suggest a tendency for individuals with autism to augment their stability during walking—and, therefore, that autistic children have a more unstable gait compared with typical children. [30, Rank 3]

Compared with typical individuals, children and adults with autism have, on average, been reported to exhibit increased instability during both standing and walking, atypical kinematics with respect to various movements, poor fine motor control as illustrated by atypical handwriting and, when making goal-directed or point-to-point arm movements, increased preparation and execution times. These findings, which are highly reliable and robust over many studies, suggest that, at a low level of cognitive processing, autistic individuals are likely to make movements which deviate from those made by individuals without autism. Adopting a bottom-up view, it is plausible that these 'low level' movement differences might impact on 'higher level' processing. This does not rule out that separate difficulties also exist at a higher level. However, it is possible that a bottom-up account would result in a parsimonious explanation of at least some of the symptoms of autism.

> **"Core social communication symptoms may be useful in identifying very young and cognitively delayed children with ASD, whereas atypical imitation, play, and motor movements may be seen in both ASD and GLOBAL DEVELOPMENTAL DELAY."**

How Movements Influence Socio-Cognitive Processes in Autism

Watching another person perform a movement evokes activity (often referred to as 'motor resonance') in one's own motor system. Just as perception influences action, action influences perception. For example, inducing a motor load through performance of a concurrent task has been shown to modulate perceptual judgements about the weight of an object being lifted by an actor or speed of a walker. Similarly, perceptual judgements can be impaired through application of disruptive transcranial magnetic stimulation to motor regions. Furthermore, in clinical populations, deficits in action production resulting from either cortical lesions and/or apraxia are correlated with deficits in action recognition. Thus, there is widespread evidence that the motor and visual systems are intrinsically linked and mutually influence each other. [31, Rank 4]

Theoretical accounts predict that

motor similarity should promote mental state inference. One study tested this hypothesis in children with respect to a particular mental state: confidence. In an initial execution condition, participants performed a visual discrimination task wherein they successively viewed two images, one a target and one a foil. Participants indicated whether the first or second image contained the target by picking up a marble and placing it in the appropriately labelled slot, and subsequently rated their confidence in their decision. In this phase of the experiment, increasing confidence was associated with faster movements. In an ensuing observation task, participants watched a series of video clips showing the hands of anonymized actors performing the execution task and judged how confident they considered the actor to be. Researchers found that participants' judgements depended upon their own movement speed in the execution condition—if a participant watched an actor who moved faster than themselves then they were more likely to rate this actor as being confident, whereas movements performed slower than a participant's own movements were more likely to be rated as low in confidence. Participants were therefore more likely to accurately estimate confidence for movements that were similar in speed to their own movements.

Movement similarity has been associated with positive affect. For example, one study found that children reported greater enjoyment and interest when observing dance movements from within their own motor repertoire, and an associated body of literature suggests that behavioural correlates of motor resonance such as movement synchronicity and automatic imitation may be intrinsically rewarding. For instance, it was demonstrated that participants who tapped synchronously with an experimenter liked the experimenter more than participants who tapped asynchronously. It can be argued that synchronicity of movements between interactants can promote the development of positive attitudes. Similarly, numerous studies have demonstrated that being imitated increases positive evaluations of interactions, and after being imitated people are more helpful, increase the amount they donate to charity, and feel closer to others. Thus, a number of studies support the notion that movement similarity and behavioural correlates of motor resonance, such as movement synchronicity and automatic imitation, promote positive affect. [32, Rank 3]

Movement Similarity and Imitation in Autism

Several researchers investigated the link between action execution and automatic imitation of others' actions in chil-

dren with autism and a matched group of typically developing children. In an action execution condition, participants were required to pick up a piece of paper and place it in a container, or pick up a piece of food and eat it. During both actions, the activity of the mouth-opening mylohyoid (MH) muscle was recorded using electromyography. In a separate 'observation condition' participants passively observed a typical child pick up a piece of (i) food and place it in their mouth or (ii) paper and place it in a container while activity from the MH muscle was recorded. It was found that during the execution condition, MH muscle activity from typical children started to increase several hundreds of milliseconds before their hand grasped the food. It continued to increase during actual grasping, and reached its peak when the child started to open its mouth. MH muscle activity for autistic children was strikingly different: no activity increase was found during the entire reaching and grasping phases; the muscle only became active as the food was brought to the mouth.

These group differences during action execution translated into group differences during action observation: for typical children MH activity was observed when they passively observed another child reach and grasp a piece of food. By contrast, the autistic children did not show MH activation during the observation of either reaching or grasping phases. Thus, atypical action execution in autistic children (i.e. a lack of anticipatory activation of the MH muscles when bringing food to their own mouth) was associated with atypical imitative responses. [33, Rank 3]

Relation Between Movement Atypicalities and Autistic Cognition

Researchers argue that, though movement atypicalities may not explain all features of autistic behaviour, the role of movements in autistic socio-cognitive function should not be overlooked.

Contemporary accounts of autism suggest atypical computations that may pervade many cognitive functions from visual perception to decision-making. Recent examples are the notions of atypical priors and aberrant precision of sensory information. The latter, for instance, proposes that the precision of (i.e. reliability or confidence attributed to) incoming sensory information is too high relative to the precision of prior beliefs. This account provides a compelling explanation for visual perceptual atypicalities in autism: for instance, suggesting that autistic individuals' immunity to many visual illusions may be due to abnormally high precision attributed to incoming sensory information relative to prior beliefs.

In addition, it has been argued that this account may help to explain difficulties with social interaction due to the heavy reliance of social interactions on prior beliefs. Although the aberrant precision account has also been extended to repetitive and stereotyped behaviours, further work would be required to apply this account to the wide-ranging movement atypicalities. However, it is not impossible to imagine such an account. With respect to the atypically jerky gait characteristic of autism, the ability to walk in a smooth fluid manner is learned and refined during early development. This process can be recast within a predictive coding framework whereby prior beliefs about how to optimally move are refined according to incoming sensory information. Atypically jerky gait in autism could therefore conceivably be due to an imbalance in the precision of incoming sensory information relative to prior beliefs. [34, Rank 5]

Biological Environmental Risk Factors in Autistic Spectrum Disorder

Investigated biological environmental risk factors in ASD include maternal and paternal age, fetal environment (e.g., sex steroids, maternal infections/immune activation, obesity, diabetes, hypertension, or ultrasound examinations), perinatal and obstetric events (e.g., hypoxia), medication (valproate, selective serotonin reuptake inhibitors), smoking and alcohol use, nutrition (e.g., short inter-pregnancy intervals, e.g., vitamin D, iron, zinc, and copper), vaccination, and toxic exposures (air pollution, heavy metals, pesticides, organic pollutants). Surprisingly, the role of potentially protective factors such as folate and fatty acid intake and levels are far less frequently examined. Considering the psychosocial environment, the relevance of extreme psychosocial institutional deprivation and maternal stress during flight and immigration has been invetsigated in relation to atypical behavior development, including autistic features. While there are many postulated mechanisms through which these environmental factors might generate autistic behaviors and clinical variants of ASD, inflammation and immune activation, oxidative stress, hypoxia, and endocrine disruptions are likely the most pivotal in contributing to atypical neurodevelopment. Although the relevance of these factors may not be directly causal, but confounded by genetic factors, understanding is limited by the paucity of research examining gene–environment interactions. [35, Rank 5]

Parental Age

Numerous environmental prenatal exposures present within the immediate environment of the developing fetus such as sex hormone alterations, maternal obesity, diabetes, hypertension, infections and immune activity, and ultrasound exposure have been considered in the context of ASD etiology. While the origins of these risks might be in genetic disposition, environmental interactions involving both the mother and fetus with the potential to compromise the fetal–maternal–placental system cannot be ignored. Many of these factors may be the product of the combination of several underlying pathophysiological processes, such as the negative effects of imbalanced fetal sex hormone exposure during critical time windows on gene transcription and expression, and subsequent neurotransmitter, neuropeptide, or immune pathways. Obesity bears an independent risk for obstetric complications, coronary heart disease, being overweight, diabetes, and several other medical conditions in the offspring.

Hypertension

At a population prevalence of approximately 10%, high blood pressure disorders are one of the most common pregnancy complications. These disorders include chronic hypertension (essential/secondary), white-coat hypertension, masked hypertension, transient gestational hypertension, gestational hypertension, and preeclampsia (de novo or superimposed on chronic hypertension), with pregnancy-related onset typically occurring in the second trimester. [36, Rank 3]

Infections and Immune Activation

Since the detection of the association between autism and congenital rubella infection, the role of infections and the immune system in the etiology of autism has been debated. Accumulating evidence suggests that the immune system and abnormal immune function, including inflammation, cytokine dysregulation, and anti-brain autoantibodies, influence trajectories of autism, playing a role in its etiology in at least a subset of cases. In addition to rubella, there are a number of other maternal viral and bacterial infections associated with ASD risk. In particular, maternal influenza bears a twofold risk for autism in offspring. While maternal infection in the presence of fever correlates with risk of ASD, this is attenuated by the use of antipyretic drugs.

The relevance of the pathogenesis of maternal infection to ASD risk may not be associated with the presence of viruses or

bacteria per se, but in the immune response they invoke, a conclusion supported by research identifying elevated inflammatory markers and antibodies in pregnant women with autistic offspring. [37, Rank 3]

Prospects and Challenges in Global Epidemiological Research of Autism

Because significant costs are associated with prevalence studies, some have questioned whether country-specific estimates should be a priority, especially where resources are limited and priorities include preventable life-threatening conditions. Such epidemiological studies are useful, however, for assessing needs and priorities within each community. Epidemiological studies often provide systematic information regarding the availability, quality, and accessibility of existing services. These studies also require development of valid tools for systematic clinical characterization, including screening and/or diagnostic instruments that can be useful for immediate improvements in training, services, and awareness, as well as facilitating future research. As such, epidemiological research may be viewed as a systematic framework for unveiling local burden and informing policy and research. [38, Rank 3]

The power of epidemiological research extends well beyond the communities in which it is conducted, particularly in view of mounting speculation regarding time trends and the potential impact of geographical and socioeconomic factors on the prevalence and possibly on the incidence of autism. While research within a global context is likely to help address such perplexing puzzles, currently, available evidence is extremely limited. There is also a clear need for better theoretical and experimental modelling to test the possible mechanisms through which various factors may have an impact on incidence, clinical presentation, or both. Studies using comparable methodology to estimate prevalence across different geographical regions and to monitor changes to it over time provide a powerful approach. Such findings may address whether certain factors, environmental or otherwise, operating in specific regions, have a disproportionate

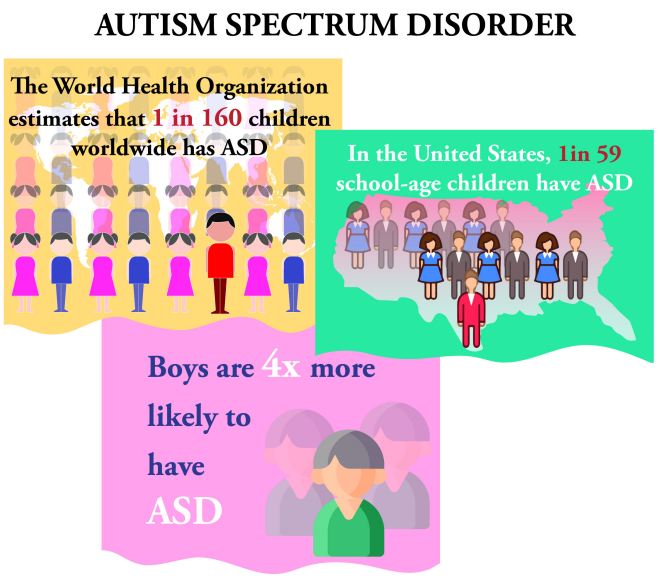

Figure 9: Facts about Autism Spectrum Disorder

impact on prevalence over time as well as ascertain the true global burden of the condition. Moreover, epidemiological studies can be potentially translated into public health practices through developing or validating screening and diagnostic methods and though strengthening capacity for services. [18, Rank 5]

Conclusion

Based on already available knowledge indicating that autism is not limited to high-income countries; the need for services especially in low and middle-income countries is felt more than before. It is imperative to engage community resources and more peripheral extensions of health systems as well. The situation in low- and middle- income countries appears to be that child health programs focus mainly on child survival issues. Very little attention is paid to developmental disabilities at policy and implementation level and as a result budget allocations and human resource deployment is directed away from these programs. Dysfunctional health systems contribute further to lack of service delivery for children with developmental disabilities. Where they exist, access to these facilities is also hindered by lack of effective identification and referral programs.

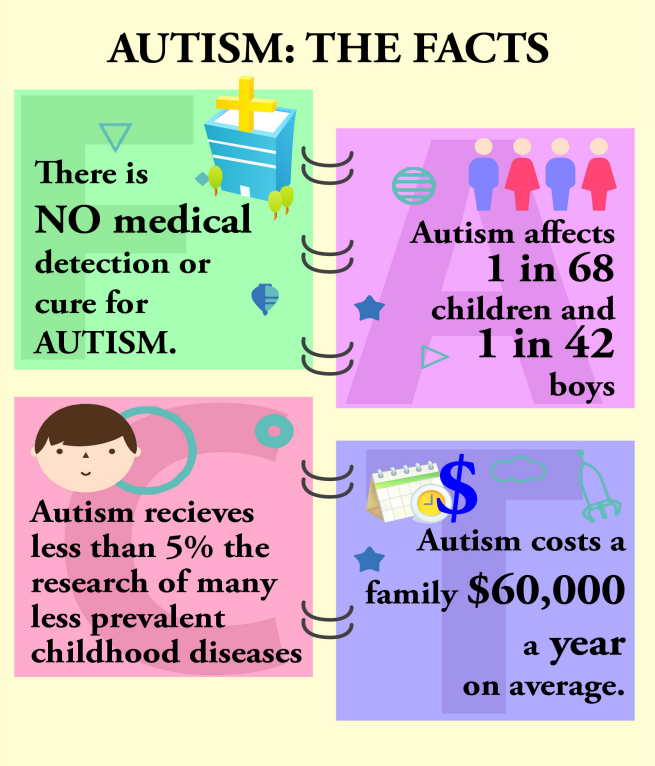

Figure 10: AUTISM and Facts

An even bigger barrier has been the lack of an evidence-based, affordable, package of care for children with autism, which could be delivered if such facilities were available. Increase in prevalence estimates over time most likely represent broadening of the diagnostic concepts, diagnostic switching from other developmental disabilities to autism, service availability, and awareness of autistic spectrum disorders in both the lay and professional public. This has clear public health implications that services for different categories of developmental disorders should not be segregated prematurely and health systems need to consider overarching programmes to fill the gap for all developmental disorders. [40, Rank 5]

*Important information for post-test is highlighted in red letters, boxes and diagrams.

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