Pharmacological Reports
https://doi.org/10.1007/s43440-021-00244-0

REVIEW

What is autism?

Priya Joon[1] · Anil Kumar[1] · Milind Parle[2]

Received: 18 September 2020 / Revised: 2 March 2021 / Accepted: 4 March 2021
© Maj Institute of Pharmacology Polish Academy of Sciences 2021

Abstract
The term "Autism spectrum disorder" (ASD), in vogue at present, has evolved after continual substantial developments taking place over more than a century. ASD is a heterogeneous, multi-factorial, developmental disability in which an unusual pattern of development takes place during infant and toddler years. As per DSM-5, Autism spectrum disorder is a combined phrase for a family of complex developmental disabilities inclusive of "Autistic Disorder, Pervasive Developmental Disorder not Otherwise Specified (PDD-NOS), and Asperger's Disorder". "ASD is characterized not only by persistent impairments in reciprocal social communication and social interactions, but is also manifested by restricted, repetitive patterns of behavior, interests, or activities". The classical clinical signs that exist in two major domains, viz. the '*social domain'* and the '*behavioral domain'* for the precise diagnosis of ASD have been tabulated and major differences between DSM-5 and DSM-4 are depicted with the help of a figure in this basic review article. A sharp rise in the incidence of ASD cases has been observed worldwide owing to various risk factors such as genetic predisposition coupled with adverse environmental conditions, gynecological interventions, etc. Two official manuals viz. the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) (published by the American Psychiatric Association), and the "International Classification of Diseases" (ICD) (published by the World Health Organization) is being regularly updated to facilitate diagnosis of ASD. ICD-11 guidelines being prospectively implemented with effect from January 2022 have attracted global attention.

Keywords ASD · DSM-5 · ICD-11 · Developmental disability

Abbreviations

ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
APA	American Psychiatric Association
ASD	Autism spectrum disorder
CBT	Cognitive behavioral therapy
CGH	Comparative genomic hybridization
CNS	Central nervous system
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth edition
EEG	Electroencephalogram
ICD	International Classification of Diseases
ICD-11	Eleventh revision of International Classification of Diseases
MRI	Magnetic resonance imaging
PDD-NOS	Pervasive developmental disorder not otherwise specified
SNP	Single nucleotide polymorphisms
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

✉ Anil Kumar
kumaruips@yahoo.com

[1] Pharmacology Division, University Institute of Pharmaceutical Sciences (UIPS), Panjab University, Chandigarh 110014, India

[2] Pharmacology Division, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar (Haryana), Pharmacy University (DPSRU), Residence: D-2, New Delhi, India

Introduction

Developmental disability means a severe, chronic disability of an individual attributable to a mental or physical impairment alone or in combination, which begins during the developmental period and is likely to continue indefinitely resulting in substantial limitations in social,

Author copy

Published online: 10 March 2021

occupational, and day-to-day functioning. Developmental disorders include attention-deficit hyperactivity disorder (ADHD), autism, learning disabilities, intellectual disability, motor disorders, cerebral palsy, Asperger's disorder, Rett syndrome, and impairments in vision and hearing. Mental disorders are conditions that affect the thinking process, feelings, mood, and behavior. These may be temporary or long-lasting. Mental disorders include depression, anxiety, bipolar disorder, personality disorder, schizophrenia, dementia, etc. To simplify the diagnosis of mental disorders, two main official manuals are being published from time to time. These are the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) compiled by the American Psychiatric Association, and the "International Classification of Diseases" (ICD) circulated by the World Health Organization. Both of these manuals are popular among clinicians in different countries of the world, while DSM is favored in America, whereas ICD is publicized in European countries. The term "Autism Spectrum Disorder" (ASD) commonly used today has evolved after more than a century. Substantial developments have taken place since then to conceptualize and understand the term "Autism". The word "autism" is originated from the Greek word "autos", synonymous with self-isolated or automatic movement [1]. Autism spectrum disorder is a heterogeneous, multi-factorial [2], developmental disability in which an unusual pattern of development takes place during infant and toddler years. The child suffering from this disorder prefers to keep itself isolated from the surrounding interactions [3]. What distinguishes autism from other neurodevelopmental disabilities is the divergence in place of delayed growth [4]. However, intellectual impairment and ASD often occur simultaneously. As per DSM-5, Autism Spectrum Disorder (ASD) is a combined phrase for a family of complex developmental disabilities inclusive of "Autistic Disorder, Pervasive Developmental Disorder not Otherwise Specified (PDD-NOS), and Asperger's Disorder". "ASD is characterized not only by persistent impairments in reciprocal social communication and social interactions, but is also manifested by restricted, repetitive patterns of behavior, interests, or activities". These clinical signs are observed from infancy till late years of life and evoke severe deficits in social, professional, or essential functional domains. However, the symptoms may not be completely apparent until community expectations surpass restrained abilities [5]. Core diagnostic traits/ attributes are apparent in the developmental phase, but some of the symptoms could be masked/ obscured by intervention, compensation/treatment, and special supports. Despite thorough research of more than 100 years in the area of developmental disorders, no reliable biomarker has been identified for accurate diagnosis of autism. Wherefore, ASD continues to be diagnosed concretely only based on the symptoms categorized in the domains of social skills and behavioral patterns, assisted by the experience narrated by the caregiver. The present review article focuses on the evolution of the concept of ASD, its prevalence in general, male: female preponderance, Indian scenario, symptoms, diagnosis, and forthcoming ICD-11 guidelines.

Prevalence

Autism has aroused great interest among investigators because it is a life-long liability and there is no cure to date. A sharp rise in the occurrence of ASD cases worldwide has been observed in recent years [6–9]. Most of the increase in prevalence can be attributed to improved diagnosis of autism and heightened awareness in society [10]. Right estimates of the incidence of ASD are critical for every nation to evaluate the burden of economic and health services to allocate appropriate funds and services to children with ASD and their families [11]. These data can be used by child health care professionals, academicians, scientists, social workers, and government agencies to formulate strategies to secure an early recognition of ASD and predict society requirements [12]. It is essential at this stage to understand the two terms: "Incidence and Prevalence" clearly, because these are often used interchangeably and erroneously. These two terms are different and convey different meanings altogether. The "incidence of a disease indicates the number of new cases diagnosed with the disease over a specified period in a defined group of people". "Prevalence reflects the number of existing cases of the disease over a specific period in a defined group of people". Incidence is expressed as the number of newly added cases, while prevalence is expressed as a percentage of existing cases in a healthy population [13]. Continuous epidemiological surveys are being carried out to measure the prevalence of ASD over the last three decades globally. Regular surveillance of autism cases in different countries revealed a steady rise. In 2016, approximately 62 million ASD patients were reported globally. According to the estimates of "Autism and Developmental Disabilities Monitoring (ADDM) Network", 1 per 59 (1.7%) children aged eight-year were diagnosed with ASD [12]. In 2011, ASD prevalence was 1% in the United Kingdom (UK) [14], whereas, in the United States of America (USA), the latest ASD prevalence estimate was 1.85% among eight-year-old children [12]. The prevalence of ASD in European countries is almost equivalent, with 1 per 89 kids afflicted by ASD [9, 15]. There are several reports available in the literature indicating that the incidence of ASD is much higher in males as compared to females. However, ASD male: female ratios/ proportion show substantial variation within the range of 8:1 [16] to 2:1 [17]. This heterogeneity is currently little studied and therefore poorly understood. "Autism and Developmental Disabilities Monitoring (ADDM) Network" of

Author copy

USA consistently estimated a male: female preponderance of 4.5:1 during the period 2006–2012 [18]. Some studies reported the male–female ratio of children suffering from ASD to be 4.3:1 [12, 19]. Males are four times more susceptible to be diagnosed with ASD as compared to females [8, 20]. The male–female ratio was found to be closer to 3:1 in yet another study [21]. This substantial sex dimorphism in male: female preponderance of ASD prompted researchers to conduct ASD studies predominantly on male patients. There is insufficient documentation of female cases suffering from autism because ASDs may go un-noticed, misdiagnosed, or diagnosed at a later stage in girls [21, 22]. Studies have indicated that there could be a disparity in prevalence because females disguise their clinical signs [20]. A 'female protective effect' is being supported by recent studies as an explanation for the higher prevalence of ASD in males as compared to females [23]. Autism cases are found to appear in all racial and ethnic populations, whether in developed or undeveloped countries. The prevalence estimates of autism in Asian patients aged 0–17 years were revealed to be 0.09% in India, 0.15–0.8% in Bangladesh, and 1.07% in Sri Lanka as per a well-designed survey [24]. The "Center for Disease Control" reported that approximately 185 per 10,000 in the USA, 152 per 10,000 in Canada, 161 per 10,000 in Japan and 100 per 10,000 children in France suffered from autism, whereas Italy, Holland, and Germany, showed the smallest degree of prevalence [25]. India is a heavily populated nation of nearly 1300 million people, out of which approximately 430 million comprise children ranging from 0 to 15 years of age. In India, more than 2 million children are likely to be afflicted by ASD [26]. In children aged $\leq$ 10 years, the preponderance of autism in India was observed to be 15 per 1000 cases, out of which maximum cases were reported from villages [27]. However, an independent study reflected a little difference in the incidence of ASD in rural areas from urban areas. The systematic survey carried out in the urban areas unfolded a cumulative prevalence of 0.09% in children aged 0–15 years; while the non-urban areas exhibited a cumulative prevalence of 0.11% in 1–18 years old children [28]. These studies are based upon documented clinical evidence [29, 30]. It is possible that there is insufficient documentation and missed diagnosis of this complex disorder occurring in infants [28].

Historical background

While autistic behavior already existed since ancient times, it is only in the last eight years [DSM-5] that it has been precisely recognized, obtained its name as ASD, and its specific characteristics described. Paul Eugen Bleuler (a Swiss psychiatrist), Hans Asperger (an Austrian child specialist), and Leo Kanner (an Austrian-American psychiatrist and social activist) have been credited aptly for designing the foundation of the concept of ASD [31–34]. The contribution of Grunya Efimovna Sukhareva, a Russian lady-psychiatrist who initially described the disorder as schizoid psychopathy in 1925 and renamed it as autistic psychopathy in 1959, however, remained foreshadowed [35, 36]. The earliest mention of autism in Indian history predates to 1944 when a Viennese child-specialist A. Ronald, working at Darjeeling (West Bengal), used the term "abnormal children" for those who suffered from developmental disability [37]. The methods adopted by Tito's mother described in the book "Beyond the Silence: My Life, the World, and Autism" authored by Tito Mukhopadhyay, an 11-year-old boy of Bangalore suffering from autism aroused a lot of interest globally [37]. The cognizance of autism in India has witnessed enormous growth in various areas of autism lately.

Signs and symptoms of Autism

Autism is a complex neurological developmental disability with the manifestations of clinical signs in early childhood [22]. As per DSM-5, "ASD is a combined phrase for a family of heterogeneous disorders, characterized not only by persistent impairments in reciprocal social communication and social interactions, but is also manifested by restricted, repetitive patterns of behavior, interests, or activities" (Table 1). These symptoms evoke severe impairments in social, professional, or essential functional domains. However, intellectual impairment and ASD occur concomitantly [5]. ASD often looks different in different individuals. It is a neurodevelopmental disorder affecting how patients interact, behave, or engage with people around them. Although the symptoms of ASD are neurologically based, they appear as behavioral manifestations that vary depending on age, language skills, and intellectual abilities of the individuals [38]. The core symptoms of ASD have a disastrous effect on the daily functioning and quality of life of the child and its family across the lifespan [39]. There is little information about the distribution and course of ASD symptoms across the lifespan [40, 41]. The characteristics of ASD change throughout the development of the child in various phases of life, with core symptom intensity, generally reported reducing over time [42–44] whereas, during the period of adulthood, main traits remain stable [40]. Although core symptom domains may reduce in severity across the lifespan, certain symptoms such as restricted interests [43] or facial expression [41] may be more stable over time [39]. Symptom patterns can fluctuate throughout the development of the child suffering from autism, with new ASD symptoms arising throughout the lifespan [39]. As the child advances in age, its social activities demand active interaction and communication. The children who had been diagnosed at an early stage of life

Author copy

Table 1 Criteria for diagnosis of Autism (DSM-5)

Social communication and interaction domain	Repetitive and restrictive behavior domain
1. Deficits in social emotional reciprocity	**1. Stereotyped or repetitive speech, motor movements, or use of objects**
Abnormality in social approach	Simple motor stereotypies
Failure of normal back and forth conversation	Echolalia
Decreased sharing of interests, emotions, affect and response	Repetitive use of objects
Total lack of initiation of social interaction	Idiosyncratic phrases
2. Deficits in non-verbal communicative behaviors	**2. Excessive adherence to routines, ritualized patterns of behavior**
Poorly integrated verbal and non-verbal communication	Excessive resistance to change such as motor ritual
Abnormal eye contact and body-language	Insistence on same route or food
Difficulty in understanding and use of non-verbal communication	Repetitive questioning or extreme distress at small changes
Complete absence of facial expression or gestures	
3. Deficits in developing and maintaining relationships	**3. Highly limited, fixed interests which are abnormal in intensity or focus**
Difficulty making friends	Strong attachment to and/or preoccupation with strange objects
Apparent absence of interest in people	Excessively limited or conservative interests
Difficulties adjusting behavior to suit different situations	**4. Hyper- or hypo- reactivity to sensory input**
	Unusual curiosity in sensory aspects of environment
	Apparent indifference to heat/ pain/cold
	Adverse response to particular sounds or textures
	Excessive smelling or touching of objects
	Fascination with lights or spinning objects

undergo psychotherapy and behavioral therapy for improving social activities, thereby masking the symptoms. A few children, who are suffering from autism begin showing core symptoms when they are a few months old. Others seem to have normal development for the initial few months or years of their lives before exhibiting ASD symptoms. The social skills issues are some of the most common symptoms. A child with ASD has difficulty in connecting with others. The child may show inappropriate social interaction, poor eye contact, and compulsive behavior. Children suffering from ASD do not like to have direct eye-to-eye connection [2]. These patients exhibit stereotypic behaviors and prefer holding parent's fingers for suggesting an item of their choice [5]. They present an indifferent attitude and show an inability in understanding the intention of others. The child suffering from autism prefers to keep itself isolated from the surrounding interactions [3]. As a consequence, these children would prefer toys, showing disregard to other children and adults. They show apathy and ignorance when their name is called [38]. They are unable to concentrate and focus on particular objects. They are highly routine-specific. These children like to live "in a world of their own". They exhibit abnormal response to the way items appear, smell, feel, or taste. The children suffering from autism show learning disabilities and echolalia [38]. Children with ASD often act abnormally or have atypical interests. They are fascinated by rotating objects and like spinning the wheels of toy cars [5, 38]. They often show stereotypic behaviors like hand-flapping, rocking, jumping, or twirling and pursue these activities with no apparent purpose. They show impulsiveness and aggressive behavior, both with themselves and others [5]. They can demonstrate delays in learning mother tongue and social skills, while their ability to walk and move around is about the same as other children of their age.

Risk factors responsible for Autism spectrum disorder

ASD is a complex neurodevelopmental disability, which may be precipitated by various genetic and non-genetic factors [45]. Many environmental [46, 47], physiological [48–50], and genetic risk factors [51, 52], which alter the functional capacity of the brain, have been associated with autism. The exact etiology of Autism is not yet identified [53]. A better understanding of the genetic, molecular, and neuronal circuit aberrations occurring in the pathogenesis of autism remains to be explored [2]. The customarily accepted pathological and non-pathological conditions resulting in autism include compromised immune system, mitochondrial dysfunction [54, 55], adverse environment, and defective genes [23]. Probable risk factors of autism are summarized in Fig. 1.

Diagnosis of ASD

Diagnosis of a physical or psychological condition involves comparing the symptoms of a person with diagnostic criteria that specify the presence or absence of certain symptoms to be suitable for a specific disease diagnosis to be appropriate, along with any criteria that exclude that particular diagnosis. There are two main official sources for autism diagnosis;

Author copy

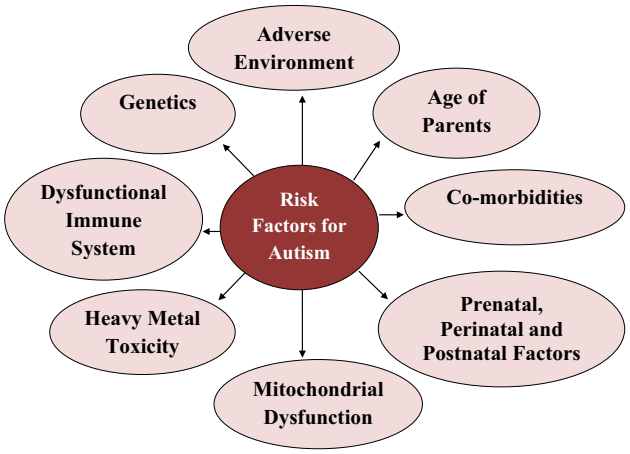

Fig. 1 Risk factors responsible for Autism

A. the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) (compiled by the American Psychiatric Association, APA), and B. the "International Classification of Diseases" (ICD) (circulated by World Health Organization, WHO). Both of these manuals are popular among clinicians in different countries of the world, while DSM is favored in America, whereas ICD is publicized in European countries.

(A) The Diagnostic and Statistical Manual of Mental Disorders (DSM) (published by the APA)

The diagnosis of ASD has been updated by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (see Fig. 2). Autism spectrum disorder encompasses disorders previously referred to as early infantile autism, childhood autism, Kanner's autism, high-functioning autism, atypical autism, pervasive developmental disorder not otherwise specified, and Asperger's disorder [5]. The revised diagnosis represents a new, more accurate, and medically useful way of diagnosing individuals with autism-related disorders. Autism spectrum disorder is a collective term for a family of heterogeneous disorders inclusive of "Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder not Otherwise Specified (PDD-NOS)". The symptoms of patients with ASD will fall on a continuum, with some patients displaying mild symptoms and others experiencing much more extreme symptoms. Manifestations of the disorder differ significantly based on the severity of the autistic syndrome, developmental level, and chronological age; hence, the term "spectrum" [5]. Individuals with ASD appear to have communication difficulties, such as reacting inappropriately to conversations, misreading non-verbal interactions, or having trouble developing age-appropriate friendships. Additionally, patients suffering from ASD can be excessively routine-dependent, extremely sensitive to changes in their surroundings, or

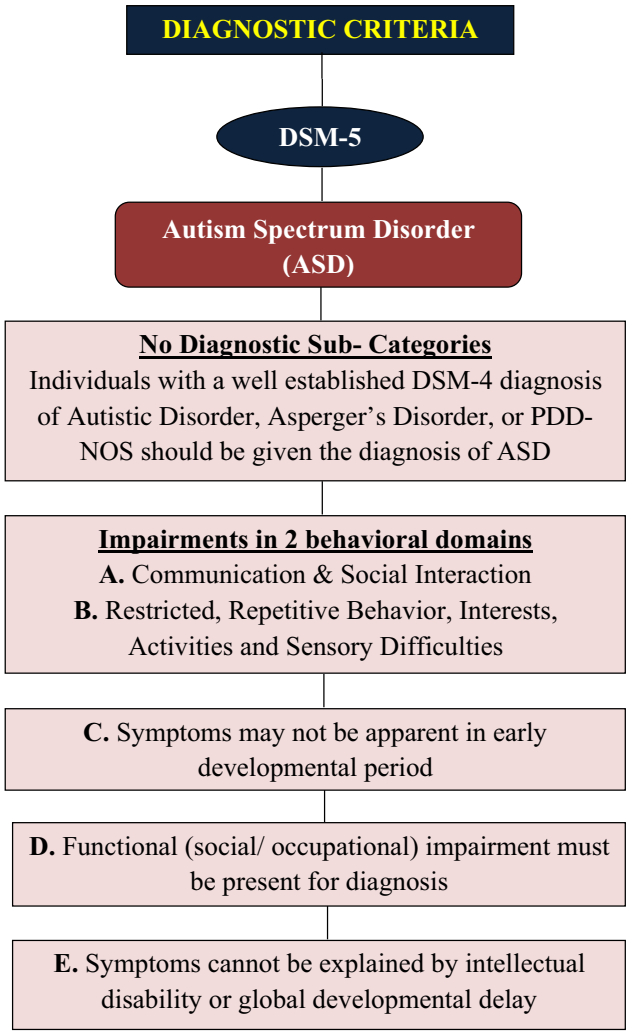

Fig. 2 Diagnostic Criteria as per DSM-5

strongly focused on inappropriate things. DSM-5 classified these symptoms into two domains: the '*social communication and interaction domain'*, including deficits in verbal and non-verbal communication, and the '*restricted, repetitive behavior domain'*. The social-communication domain is monothetic and the restricted, repetitive behaviors domain is polythetic. For a formal diagnosis of ASD, children should demonstrate symptoms across all three clusters in the first domain of social communication and interaction, and two symptoms from any of the four symptoms-groupings in the second domain of restricted, repetitive behavior (Table 1). Core diagnostic features exhibiting functional difficulties are visible in the early developmental period, but intervention and support strategies aimed at improving a child's behavior and communication may compensate for difficulties at least in some contexts. Early diagnosis of ASD helps in providing behavioral therapies to the affected people. Standardized behavioral diagnostic methods with good psychometric

Author

properties, including interviews with caregivers, questionnaires, and clinician observation assessments, are available and can enhance the reliability of diagnosis over time and across clinicians. Misconceptions about ASD and lack of knowledge of diagnostic criteria can lead to misdiagnosis in two directions: over-diagnosis and under-diagnosis. Without additional educational support, studying regularly in a normal public school, eating lunch-box, and doing homework become challenging. If severe gross motor or fine motor delays are present, other diagnoses should also be considered [5]. Co-morbid intellectual impairment, developmental co-ordination disorder, structural language disorder, anxiety disorders, depressive disorders, ADHD, and other psychiatric disorders may co-occur with autism, which must also be taken care of by physicians while diagnosing ASD. The Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) constitute gold standards for formal diagnostic assessments of ASD. ADI-R is a semi-structured interview for caregivers of alleged autism cases [56], whereas ADOS involves observation of social behavior, communication, and play by ADOS certified therapists [57]. According to the American Academy of Pediatrics Council of Children with Disabilities, all patients with ASD should undergo a physical and a neurological examination, an audiogram, and a tympanogram [58]. A metabolic workup is requested only if a metabolic disease is suspected. Brain magnetic resonance imaging (MRI) is recommended if tuberous sclerosis is suspected or the neurological examination reveals abnormalities. An electroencephalogram (EEG) should be done if a history of seizures exists. In boys, testing for fragile X is prescribed in case of a family history of cognitive impairment. In females, MECP2 gene testing must be undertaken to rule out Rett syndrome [59]. Chromosomal microarray analysis, exome sequencing [60], and genetic testing are reliable methods for the detection of de novo mutations and ASD risk genes [61]. Currently, it is recommended to perform Comparative genomic hybridization (CGH) and single nucleotide polymorphisms (SNP) microarray studies to determine gene micro-duplications or micro-deletions associated with ASD [62]. A recent advancement is the automated electroencephalogram-based diagnosis of ASD using three different computational paradigms of signal processing such as wavelets, neural networks, and nonlinear analysis and chaos theory [3, 63–65]. The diagnosis of ASD is categorized by the problems an individual has concerning social communication and restricted or repetitive behaviors. ASD has been divided into three distinct levels. By defining a patient's diagnosis of ASD as Level 1, Level 2, or Level 3, the degree of support needed to help the patient live a satisfactory and independent life can be determined precisely [5].

Level-1 (ASD)—It refers to mild autism. Patients who qualify as having level-1 ASD may struggle in social situations and have some concerns about restrictive or repetitive behaviors but need only minimal support in their day-to-day activities to function. Possibly they can communicate verbally. They may, however, struggle to sustain a conversation. It is difficult for them to make and keep friends. They may prefer to adhere to their existing routines and feel uncomfortable with changes or unpredictable events. They would want to do certain things in their way.

Level-2 (ASD)—It refers to the middle level of ASD, which typically requires substantial support in some areas. People with level-2 ASD have greater social skills problems and may not be able to communicate verbally. If they do communicate, their discussions are confined to specific topics. They will need substantial help to engage in social activities. People with level 2 ASD can be more atypical of nonverbal actions than most of their peers. They might not make a lot of eye contact. They do not convey feelings in the same way that most other people do, by the tone of voice or facial expressions. They struggle more with their restrictive and repetitive behaviors. If they are not permitted to obey their routines or habits they become very unhappy or upset.

Level-3 (ASD) —Level-3 ASD is the most severe level of ASD that needs very significant care to help the person conduct everyday life tasks that are vital to social or behavioral abilities. People with level 3 ASD show significant social communication and social skills difficulties. Some people with level 3 ASD may interact verbally (through words), but many individuals do not orally interact or use a lot of words. They often struggle with unforeseen events. They may be excessively sensitive to specific sensory input. They have restrictive or repetitive behaviors like rocking, echolalia, spinning things, or other activities that affect their focus.

(B) The International Classification of Diseases (ICD) (published by the WHO)

An update of the chapter on "Mental, Behavioral and Neurodevelopmental Disorders" in the 11th revision of the "International Classification of Diseases and Related Health Problems" (ICD-11), published by WHO for prospective implementation from January 2022 is eagerly awaited globally. In June 2018, the WHO released a draft of the ICD-11 to its 194 member states, for review and preparation for implementation. The World Health Assembly has approved the ICD-11 guidelines at its meeting held in May 2019 [66, 67]. ASD has undergone considerable diagnostic evolution over the past several decades. Continual improvements in the definition and diagnostic criteria of Autism spectrum disorder have been documented since infantile autism (in DSM-3, 1980) through autistic disorder (in ICD-10, 1992), pervasive development disorder (in DSM-4, 1994) to autism spectrum disorder (in DSM-5, 2013) [1]. Sustained efforts of both the bodies, the World Health Organization on the

Author copy

ICD-11 and the American Psychiatric Association on the DSM-5 have been directed towards making an accurate diagnosis of the diseases based on uniform (specified) criteria to advocate rational drug therapy, thereby benefitting society at large. During the development of the chapter on "Mental, Behavioral or Neurodevelopmental Disorders" in ICD-11, a particular focus is placed on clinical utility and global applicability [68] of these updated guidelines to offer a stronger framework for the WHO member states and healthcare practitioners to reduce the global burden on mental health [67]. Given the recent approval of the ICD-11 by the World Health Assembly and its ongoing implementation all over the world, a range of concerns arises about the overall status of nosology of mental disorders as well as changes in the diagnostic criteria for particular conditions and the consequences of these revisions for research and practice. ICD-11 guidelines are being refined to address the following questions in particular. Will updating the classification of mental disorders reinforce health practice and research? How useful is the proposed implementation of the ICD-11, with its revised chapter on "Mental, Behavioral or Neurodevelopmental disorders" to the clinicians and fruitful to the patients? [67]. The term "neurodevelopmental disorders" has a strong history, yet it had not been included in previous editions of the ICD or the DSM. The term "neurodevelopmental disorders" applies to a category of disorders that (1) exhibit early-onset, (2) affect both cognitive as well as social-communicative development, (3) have a multi-factorial origin, (4) display important sex differences, where males are more commonly affected than females, (5) have a chronic course with impairments generally lasting into adulthood [69]. This term "neurodevelopmental disorders" differentiates these disorders from other more common childhood disorders, such as ADHD, anxiety, and mood disorders that are believed to result from some form of psychosocial adversity and are more episodic. In the ICD-11, "neurodevelopmental disorders" comprise of "(1) Disorders of intellectual development, (2) Developmental speech or language disorders, (3) Autism spectrum disorder (ASD), (4) Developmental learning disorders, (5) Developmental motor coordination disorder, (6) Attention deficit hyperactivity disorder (ADHD), (7) Stereotyped movement disorder, and (8) a remainder category labeled as other neurodevelopmental disorders". In the ICD-11, both ASD and ADHD may co-exist in the same individual, which is a significant and extremely beneficial refinement [66]. The mounting evidence also suggests that ASD and ADHD have similar genetic variations, related psychological deficiencies, and neuro-imaging parameters [70]. The age of onset for ASD is now in the early developmental period rather than being specified as having an onset before 3 years of age. By and large, various changes in the ICD-11 at the classification level and the disorder description level resulted in a greater agreement with the DSM-5. The DSM-5 is regarded to be the "gold standard in ASD diagnosis" and the ICD-11 guidelines closely mirror the DSM-5 approach, but do distinguish autism with and without intellectual disabilities [71]. ICD-11 guidelines for ASD have been substantially revised to reflect the existing literature, including the life-long presentations of ASD. Furthermore, specifiers are presented to indicate the co-occurrence of impairments in general cognitive functioning and functional language skills to capture the full spectrum of ASD presentations in a more dimensional manner, which are critical for guiding treatment selection [66, 71]. Overall, the several revisions suggested in the "Mental, Behavioral, or Neurodevelopmental Disorders" chapter of the ICD-11 represent a major improvement in diagnostic classification of mental disorders as well as in mental health research [67].

Treatment of Autism

Therapeutic management of patients suffering from ASD is challenging. Pharmacological treatment of basic symptoms of ASD is by and large intricate, owing to the complexity in the appearance of ASD, co-morbid conditions, and age-related response variability [39]. Despite the urgent need for a satisfactory remedy, there is no US-FDA-approved medication, to heal the core symptoms of ASD, particularly defective social skills and abnormal behavior [72–74]. However, several clinical studies, which successfully diminish the severity of ASD-associated secondary symptoms as well as co-morbidities are available in the literature [75–78]. At present, non-pharmacological interventions [79–81] inclusive of cognitive-behavioral therapy (CBT) [82], nutritional therapy [83–86], and herbal therapy [87–90] aimed at improving the quality of life of the patient are being adopted. The benefits of stem cell therapy are also being investigated to reduce family distress [9, 91]. Since the present review article covers fundamental elements of autism, a separate compilation focusing on the management of non-core symptoms associated with ASD and the potential targets helpful in discovering new medicines for reversing core symptoms is envisaged.

Concluding remarks

What distinguishes autism from other developmental disabilities is the divergence and not the delayed growth. The concept "Autism Spectrum Disorder" (ASD), which is popular today, has evolved after substantial developments that have been continuously taking place over more than a century. Sustained efforts of both the bodies, the WHO on ICD-11 and the APA on DSM-5 have been directed towards making an accurate diagnosis of the diseases based on laid-down

Author copy

criteria to advocate rational drug therapy for the benefit of the society at large. The update of the chapter on "Mental, Behavioral and Neurodevelopmental Disorders" of the eleventh edition of ICD (to be implemented from January 2022) is envisioned worldwide with interest. At present, there is no US-FDA-approved medicine for the treatment of patients suffering from ASD. Extensive research is being carried out on multiple target sites such as glutamate/GABA imbalance, immune dysfunction, neuro-inflammation, etc. to discover efficacious allopathic medicines for the management of the core symptoms of ASD. It would be worthwhile to identify proper dietary supplements useful in alleviating ASD symptoms. Integration of nutritional approach with potentially useful allopathic medicines as well as complementary therapies administered by professional therapists tailored for each child as per its symptoms is most likely to yield optimal results. This integrated approach would pave the way for new therapeutic interventions and goals providing a ray of hope to individuals afflicted with Autism.

Acknowledgements The authors would like to thank the Department of Science and Technology, Govt. of India, New Delhi for the financial support under the INSPIRE program.

Funding This research was supported by the Department of Science and Technology (CN) (Grant DST/INSPIRE/03/2019/001467).

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Volkmar FR, McPartland JC. From Kanner to DSM-5: autism as an evolving diagnostic concept. Annu Rev Clin Psychol. 2014;10:193–212.
2. Park HR, Lee JM, Moon HE, Lee DS, Kim BN, Kim J, et al. A short review on the current understanding of autism spectrum disorders. Exp Neurobiol. 2016;25(1):1.
3. Bhat S, Acharya UR, Adeli H, Bairy GM, Adeli A. Autism: cause factors, early diagnosis and therapies. Rev Neurosci. 2014;25(6):841–50.
4. Rutter M, Schopler E. Autism and pervasive developmental disorders: concepts and diagnostic issues. J Autism Dev Disord. 1987;17(2):159–86.
5. Edition 5th. Diagnostic and statistical manual of mental disorders (DSM-5). Am Psychiatric Assoc. Washington, DC. 2013;21:50–9.
6. Hansen SN, Schendel DE, Parner ET. Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. JAMA Pediatrics. 2015;169(1):56–62.
7. DeFilippis M, Wagner KD. Treatment of autism spectrum disorder in children and adolescents. Psychopharmacol Bull. 2016;46(2):18–41.
8. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveillance Summaries. 2018;67(6):1.
9. Pistollato F, Forbes-Hernández TY, Iglesias RC, Ruiz R, Zabaleta ME, Cianciosi D, et al. Pharmacological, non-pharmacological and stem cell therapies for the management of autism spectrum disorders: a focus on human studies. Pharmacol Res. 2020;152:104579.
10. Fombonne E. Epidemiological controversies in autism. Schweiz Arch Neurol Psychiatr. 2020. https://doi.org/10.4414/sanp.2020.03084.
11. Boswell K, Zablotsky B, Smith C. Predictors of autism enrollment in public school systems. Except Child. 2014;81(1):96–106.
12. Maenner MJ, Shaw KA, Baio J. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. MMWR Surveillance Summaries. 2020;69(4):1.
13. Ratajczak HV. Theoretical aspects of autism: causes—a review. J Immunotoxicol. 2011;8(1):68–79.
14. Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J, et al. Epidemiology of autism spectrum disorders in adults in the community in England. Arch Gen Psychiatry. 2011;68(5):459–65.
15. ASDEU. Autism Spectrum Disorders in the European Union (ASDEU), 2018. http://asdeu.eu/wp-content/uploads/2016/12/ASDEUExecSummary27September2018.pdf.
16. Icasiano F, Hewson P, Machet P, Cooper C, Marshall A. Childhood autism spectrum disorder in the Barwon region: a community based study. J Paediatr Child Health. 2004;40(12):696–701.
17. Fombonne E, Du Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a French epidemiological survey. J Am Acad Child Adolesc Psychiatry. 1997;36(11):1561–9.
18. Baio J. Prevalence of Autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. Surveillance Summaries. 2014;63:1–21.
19. Van Wijngaarden-Cremers PJ, van Eeten E, Groen WB, Van Deurzen PA, Oosterling IJ, Van der Gaag RJ. Gender and age differences in the core triad of impairments in autism spectrum disorders: a systematic review and meta-analysis. J Autism Dev Disord. 2014;44(3):627–35.
20. Tubío-Fungueiriño M, Cruz S, Sampaio A, Carracedo A, Fernández-Prieto M. Social camouflaging in females with Autism spectrum disorder: a systematic review. J Autism Dev Disord. 2020. https://doi.org/10.1007/s10803-020-04695-x.
21. Loomes R, Hull L, Mandy WP. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2017;56(6):466–74.
22. Olson LA, Mash LE, Linke A, Fong CH, Müller RA, Fishman I. Sex-related patterns of intrinsic functional connectivity in children and adolescents with autism spectrum disorders. Autism. 2020;24(8):2190–201.
23. Styles M, Alsharshani D, Samara M, Alsharshani M, Khattab A, Qoronfleh MW, et al. Risk factors, diagnosis, prognosis and treatment of autism. Front Biosci. 2020;25(9):1682–717.
24. Hossain MD, Ahmed HU, Uddin MJ, Chowdhury WA, Iqbal MS, Kabir RI, et al. Autism Spectrum Disorders (ASD) in South Asia: a systematic review. BMC Psychiatry. 2017;17(1):1–7.
25. Chiarotti F, Venerosi A. Epidemiology of Autism Spectrum Disorders: a review of worldwide prevalence estimates since 2014. Brain Sci. 2020;10(5):274–94.
26. Krishnamurthy V. A clinical experience of autism in India. J Dev Behav Pediatr. 2008;29(4):331–3.
27. Raina SK, Chander V, Bhardwaj AK, Kumar D, Sharma S, Kashyap V, et al. Prevalence of autism spectrum disorder among rural, urban, and tribal children (1–10 years of age). J Neurosci Rural Pract. 2017;8(3):368–74.

Author copy

28. Chauhan A, Sahu JK, Jaiswal N, Kumar K, Agarwal A, Kaur J, et al. Prevalence of autism spectrum disorder in Indian children: a systematic review and meta-analysis. Neurol India. 2019;67(1):100–4.
29. Jain R, Juneja M, Sairam S. Children with developmental disabilities in India: age of initial concern and referral for rehabilitation services, and reasons for delay in referral. J Child Neurol. 2013;28(4):455–60.
30. Kommu JV, Gayathri KR, Srinath S, Girimaji SC, Seshadri SP, Gopalakrishna G. Profile of two hundred children with Autism Spectrum Disorder from a tertiary child and adolescent psychiatry centre. Asian J Psychiatr. 2017;28:51–6.
31. Bleuler E. The theory of schizophrenic negativism. J Nerv Ment Dis (WA White, Trans). 1912;39:50–7.
32. Kanner L. Autistic disturbances of affective contact. Nervous Child. 1943;2(3):217–50.
33. Asperger H. Die, "AutistischenPsychopathen" imKindesalter. Arch Psychiatr Nervenkr. 1944;117:76–136.
34. Edition 4th, text rev. Diagnostic and statistical manual of mental disorders (DSM-IV-TR). Am Psychiatric Assoc. Washington, DC. 2000; 495–97
35. Ssucharewa GE. Die schizoiden Psychopathienim Kindesalter. (Part 1 of 2). Eur Neurol. 1926;60(3–4):235–47.
36. Manouilenko I, Bejerot S. Sukhareva—prior to Asperger and Kanner. Nord J Psychiatry. 2015;69(6):1761–4.
37. Action For Autism: National centre for Autism in India. History of Autism in India. http://www.autism-india.org/history-autism-india.php. Accessed 5 Sept 2020.
38. Hyman SL, Levy SE, Myers SM. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics. 2020;145(1):e20193447.
39. Pandina G, Ring RH, Bangerter A, Ness S. Current approaches to the pharmacologic treatment of core symptoms across the lifespan of Autism Spectrum Disorder. Child Adolesc Psychiatr Clin N Am. 2020;29(2):301–17.
40. Siebes R, Muntjewerff JW, Staal W. Differences of symptom distribution across adult age in high functioning individuals on the autism spectrum using subscales of the autism spectrum quotient. J Autism Dev Disord. 2018;48(11):3939–44.
41. Bal VH, Kim SH, Fok M, Lord C. Autism spectrum disorder symptoms from ages 2 to 19 years: Implications for diagnosing adolescents and young adults. Autism Res. 2019;12(1):89–99.
42. Shattuck PT, Seltzer MM, Greenberg JS, Orsmond GI, Bolt D, Kring S, et al. Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. J Autism Dev Disord. 2007;37(9):1735–47.
43. Esbensen AJ, Seltzer MM, Lam KS, Bodfish JW. Age-related differences in restricted repetitive behaviors in autism spectrum disorders. J Autism Dev Disord. 2009;39(1):57–66.
44. Magiati I, Tay XW, Howlin P. Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: a systematic review of longitudinal follow-up studies in adulthood. Clin Psychol Rev. 2014;34(1):73–86.
45. Jones EJ, Gliga T, Bedford R, Charman T, Johnson MH. Developmental pathways to autism: a review of prospective studies of infants at risk. Neurosci Biobehav Rev. 2014;39:1–33.
46. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case–control analysis within the Nurses' Health Study II cohort. Environ Health Perspect. 2015;123(3):264–70.
47. Kalkbrenner AE, Windham GC, Zheng C, McConnell R, Lee NL, Schauer JJ, et al. Air toxics in relation to autism diagnosis, phenotype, and severity in a US family-based study. Environ Health Perspect. 2018;126(3):037004.
48. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309(16):1696–703.
49. Ornoy A, Weinstein-Fudim L, Ergaz Z. Prenatal factors associated with autism spectrum disorder (ASD). Reprod Toxicol. 2015;56:155–69.
50. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017;135(1):29–41.
51. De Rubeis S, Buxbaum JD. Genetics and genomics of autism spectrum disorder: embracing complexity. Hum Mol Genet. 2015;24(R1):R24–31.
52. de la Torre-Ubieta L, Won H, Stein JL, Geschwind DH. Advancing the understanding of autism disease mechanisms through genetics. Nat Med. 2016;22(4):345–61.
53. Bai D, Yip BHK, Windham GC, et al. Association of genetic and environmental factors with autism in a 5-country cohort. JAMA Psychiatry. 2019;76(10):1035–43.
54. Hughes HK, Mills Ko E, Rose D, Ashwood P. Immune dysfunction and autoimmunity as pathological mechanisms in autism spectrum disorders. Front Cell Neurosci. 2018;12:405.
55. Nardone S, Elliott E. The interaction between the immune system and epigenetics in the etiology of autism spectrum disorders. Front Neurosci. 2016;10:329.
56. Brentani H, Paula CS, Bordini D, Rolim D, Sato F, Portolese J, et al. Autism spectrum disorders: an overview on diagnosis and treatment. Braz J Psychiatry. 2013;35:S62-72.
57. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The Autism Diagnostic Observation Schedule—Generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000;30(3):205–23.
58. Khalifeh S, Yassin W, Kourtian S, Boustany RM. Autism in review. Lebanese Med J. 2016;103(3431):1–6.
59. Filipek PA, Accardo PJ, Ashwal S, Baranek GT, Cook EH, Dawson G, et al. Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. Neurology. 2000;55(4):468–79.
60. Yu L, Wynn J, Cheung YH, Shen Y, Mychaliska GB, Crombleholme TM, et al. Variants in GATA4 are a rare cause of familial and sporadic congenital diaphragmatic hernia. Hum Genet. 2013;132(3):285–92.
61. Jeste SS, Geschwind DH. Disentangling the heterogeneity of autism spectrum disorder through genetic findings. Nat Rev Neurol. 2014;10(2):74–81.
62. Beaudet AL. The utility of chromosomal microarray analysis in developmental and behavioral pediatrics. Child Dev. 2013;84(1):121–32.
63. Adeli H, Ghish-Dastidar S. Automated EEG-based diagnosis of neurological disorders: inventing the future of neurology. CRC Press; 2010.
64. Ahmadlou M, Adeli H, Adeli A. Fractality and a wavelet-chaos-neural network methodology for EEG-based diagnosis of autistic spectrum disorder. J Clin Neurophysiol. 2010;27(5):328–33.
65. Ahmadlou M, Adeli H, Adeli A. Improved visibility graph fractality with application for the diagnosis of autism spectrum disorder. Phys A. 2012;391(20):4720–6.
66. Reed GM, First MB, Kogan CS, Hyman SE, Gureje O, Gaebel W, et al. Innovations and changes in the ICD-11 classification of mental, behavioral and neurodevelopmental disorders. World Psychiatry. 2019;18(1):3–19.
67. Stein DJ, Szatmari P, Gaebel W, Berk M, Vieta E, Maj M, et al. Mental, behavioral and neurodevelopmental disorders in the

Author copy

ICD-11: an international perspective on key changes and controversies. BMC Med. 2020;18(1):1–24.
68. Reed GM, Ayuso-Mateos JL. Towards a more clinically useful International World Health Organization classification of mental disorders. Rev Psiquiatr Salud Ment. 2011;4(3):113–6.
69. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. Lancet Psychiatr. 2017;4(4):339–46.
70. Stergiakouli E, Smith GD, Martin J, Skuse DH, Viechtbauer W, Ring SM, et al. Shared genetic influences between dimensional ASD and ADHD symptoms during child and adolescent development. Mol Autism. 2017;8(1):18.
71. Gaebel W, Zielasek J, Reed GM. Mental and behavioral disorders in the ICD-11: concepts, methodologies, and current status. Psychiatr Pol. 2017;51(2):169–95.
72. Bahmani M, Sarrafchi A, Shirzad H, Rafieian-Kopaei M. Autism: pathophysiology and promising herbal remedies. Curr Pharm Des. 2016;22(3):277–85.
73. Goel R, Hong JS, Findling RL, Ji NY. An update on pharmacotherapy of autism spectrum disorder in children and adolescents. Int Rev Psychiatry. 2018;30(1):78–95.
74. Lamy M, Pedapati EV, Dominick KL, Wink LK, Erickson CA. Recent advances in the pharmacological management of behavioral disturbances associated with autism spectrum disorder in children and adolescents. Pediatric Drugs. 2020;22(5):473–83.
75. Fortea A, Ilzarbe D, Espinosa L, Solerdelcoll M, de Castro C, Oriolo G, et al. Long-acting injectable atypical antipsychotic use in adolescents: an observational study. J Child Adolesc Psychopharmacol. 2018;28(4):252–7.
76. Maneeton N, Maneeton B, Putthisri S, Suttajit S, Likhitsathian S, Srisurapanont M. Aripiprazole in acute treatment of children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2018;14:3063–72.
77. Maneeton N, Maneeton B, Putthisri S, Woottiluk P, Narkpongphun A, Srisurapanont M. Risperidone for children and adolescents with autism spectrum disorder: a systematic review. Neuropsychiatr Dis Treat. 2018;14:1811.
78. Fallah MS, Shaikh MR, Neupane B, Rusiecki D, Bennett TA, Beyene J. Atypical antipsychotics for irritability in pediatric autism: a systematic review and network meta-analysis. J Child Adolesc Psychopharmacol. 2019;29(3):168–80.
79. Accordino RE, Kidd C, Politte LC, Henry CA, McDougle CJ. Psychopharmacological interventions in autism spectrum disorder. Expert Opin Pharmacother. 2016;17(7):937–52.
80. Conner CM, White SW. Brief report: feasibility and preliminary efficacy of individual mindfulness therapy for adults with autism spectrum disorder. J Autism Dev Disord. 2018;48(1):290–300.
81. Benevides TW, Shore SM, Andresen ML, Caplan R, Cook B, Gassner DL, et al. Interventions to address health outcomes among autistic adults: a systematic review. Autism. 2020;24(6):1345–59.
82. Weston L, Hodgekins J, Langdon PE. Effectiveness of cognitive behavioral therapy with people who have autistic spectrum disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2016;49:41–54.
83. Li YJ, Li YM, Xiang DX. Supplement intervention associated with nutritional deficiencies in autism spectrum disorders: a systematic review. Eur J Nutr. 2018;57(7):2571–82.
84. Bjørklund G, Waly MI, Al-Farsi Y, Saad K, Dadar M, Rahman MM, et al. The role of vitamins in autism spectrum disorder: what do we know? J Mol Neurosci. 2019;67(3):373–87.
85. Cekici H, Sanlier N. Current nutritional approaches in managing autism spectrum disorder: a review. Nutr Neurosci. 2019;22(3):145–55.
86. Peretti S, Mariano M, Mazzocchetti C, Mazza M, Pino MC, Verrotti Di Pianella A, et al. Diet: the keystone of autism spectrum disorder? Nutr Neurosci. 2019;22(12):825–39.
87. Gonzales EL, Jang JH, Mabunga DF, Kim JW, Ko MJ, Cho KS, et al. Supplementation of Korean Red Ginseng improves behavior deviations in animal models of autism. Food Nutr Res. 2016;60(1):29245.
88. Joon P, Dhingra D, Parle M. Shatavari: a nature's gift for autism. Asian J Bio Sci. 2019;14(1 & 2):12–21.
89. Al-Gholam MA, Ameen O. The neuroprotective effect of Ginkgo Biloba extract on valproic acid induced autistic features in mice. J Clin Diagn Res. 2020. https://doi.org/10.7860/JCDR/2020/44201.13948.
90. Joon P, Dhingra D, Parle M. Biochemical evidence for anti-autistic potential of Asparagus racemosus. Int J Plant Sci. 2020;15(1):42–51.
91. Sun JM, Kurtzberg J. Cell therapy for diverse central nervous system disorders: inherited metabolic diseases and autism. Pediatr Res. 2018;83(1):364–71.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author Copy