



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article

June 2022 Vol.:24, Issue:3

© All rights are reserved by Raghavendra Rao M.V et al.

Bridge the Gap, Understanding the Needs of Emerging Adults with Autism Spectrum Disorder (ASD)



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

Raghavendra Rao M.V*¹, MM Karindas², Ilie Vasiliev³, Hitesh Lakshmi Billa⁴, Srikanth Bhandari⁵, Dilip Mathai⁶, Manick Dass⁷, Jerryson.A.Gidisu⁸, Mahendra Kumar Verma⁹

1. Department of Medicine, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India
2. Professor, Department of Oncology, world Academy of Medical sciences,
3. Professor, Department of Internal Medicine, world Academy of Medical sciences,
4. Registrar, Interventional Pulmonology, Apollo Institute of Medical Science and Research, Hyderabad, TS, India
5. Department of psychiatry, Asha Hospital, Banjara Hills, Hyderabad, TS, India
6. Professor, Department of Medicine,
7. Dean, Apollo Institute of Medical Science and Research, Hyderabad, TS, India
8. Professor, Department of Microbiology, Apollo Institute of Medical Science and Research, Hyderabad, TS, India
9. Assistant professor, American University school of medicine, Aruba, Caribbean Islands

Submitted: 25 May 2022
Accepted: 31 May 2022
Published: 30 June 2022

Keywords: Autism spectrum disorder (ASD), prevalence, screening, evaluation, Neurobiological element, intellectual disabilities (ID)

ABSTRACT

Autism is an extremely unpredictable neurodevelopmental illness. Autism is not a “disease” that can be avoidable. It is a state that originates from neurobiological elements. Children with autism spectrum disorder have signs of lower intelligence. than normal. They have difficulty learning. Other children with the disorder have normal to high intelligence Seriousness can be challenging and determined. Prevalent growing neurodevelopmental disorders are characterized by disability in communication, social interaction and repetitive attitudes. Research strongly on intimate genetics is the basis of inheritance. Autism spectrum disorder (ASD) is a condition referred to brain development that impacts how a person distinguishes with others, in social interaction and communication. The disorder encompasses repetitive behavior. The term "spectrum" in autism spectrum disorder refers to the wide range of symptoms and severity. Autism has characteristics first appearing during infancy or childhood and generally follows a steady course without suspension. It is distinguished by ongoing learning of developmental impairments in communication and social sensibility and rotenone behaviors. Autism was recognized as a disability in 2016 under the Rights of Persons with Disabilities (RPwD) Act, 2016.



HUMAN JOURNALS

www.ijppr.humanjournals.com

INTRODUCTION

ASD occurs more often in boys than girls, with a 4:1 male-to-female ratio (1).

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors (2).

This new definition is intended to be more accurate and works toward diagnosing ASD at an earlier age (3).

However, studies estimating the potential impact of moving from the (Diagnostic and Statistical Manual) (DSM)-DSM-IV to the DSM-5 have predicted a decrease in ASD prevalence (4, 5) and there has been concern that children with a previous PDD-NOS diagnosis would not meet criteria for ASD diagnosis (6, 7).

Robust empirical findings confirm these The Theory of Mind (ToM) impairments in ASD (Kimhi, 2014), based on inferior performance on assessment tasks. (8).

Research has found that people with ASD without intellectual disabilities (ID) tend to perform better on explicit ToM tasks (9).

The international scientific debate on personality pathologies in childhood is still characterized by several controversies (10, 11).

The diagnostic manual of Mental Disorders against personality diagnosis during childhood development are linked to three specific issues. (12,13).

P. Kernberg et al , Bleiberg, has revealed the existence of personality patterns that are recognizable in childhood (14,15).

History

The concept of autism was coined in 1911 by the German psychiatrist Eugen Bleuler (16).

In 1798, medical student, JeanItard treated the Wild Boy of Aveyron, with a behavioral program (17).

A Soviet child psychiatrist, Grunya Sukhareva, described a similar syndrome that was published in Russian in 1925, and in German in 1926 (18).

In 1938, Hans Asperger popularized the word. ASD is now known as Asperger syndrome (19),

.The word *autism* first took its modern sense in 1938 Leo Kanner first used *autism* in its modern sense *infantile autism* in a 1943. Kanner's first paper, "autistic aloneness" is regarded as typical of the autistic spectrum of disorders. (20).

In the late 1960s, autism was established as a separate syndrome (21).

SYMPTOMS

Poorly developed social skills

Difficulty with expressive and receptive communication.

A child or adult with ASD may have problems with social relationships and connection skills.

Fails to answer to his/her name.

Prefer playing alone, retreating into his or her own world.

Has substandard eye contact and deficiency of facial expression.

Unable to speak or has delayed speech, or loses the capacity to say words or sentences.

Can't start a discussion.

Speaks with an unusual voice and may use a monotonous voice or machine-like speech.

Replay the word letter for letter, but doesn't understand how to make use of them.

Unable to understand easy questions.

Unable to understand and communicate emotions.

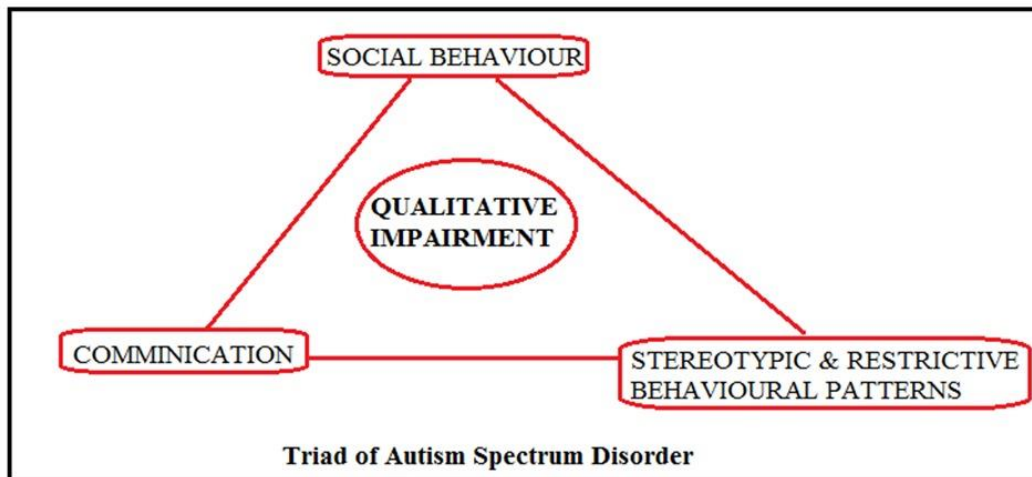
Doesn't bring intentions to contribute interest.

ASD behavior

- Performs repetitive movements.
- Execute activities that could bring about self-damage/ punishment
- Has problems with coordination in movement, such as walking on toes, and

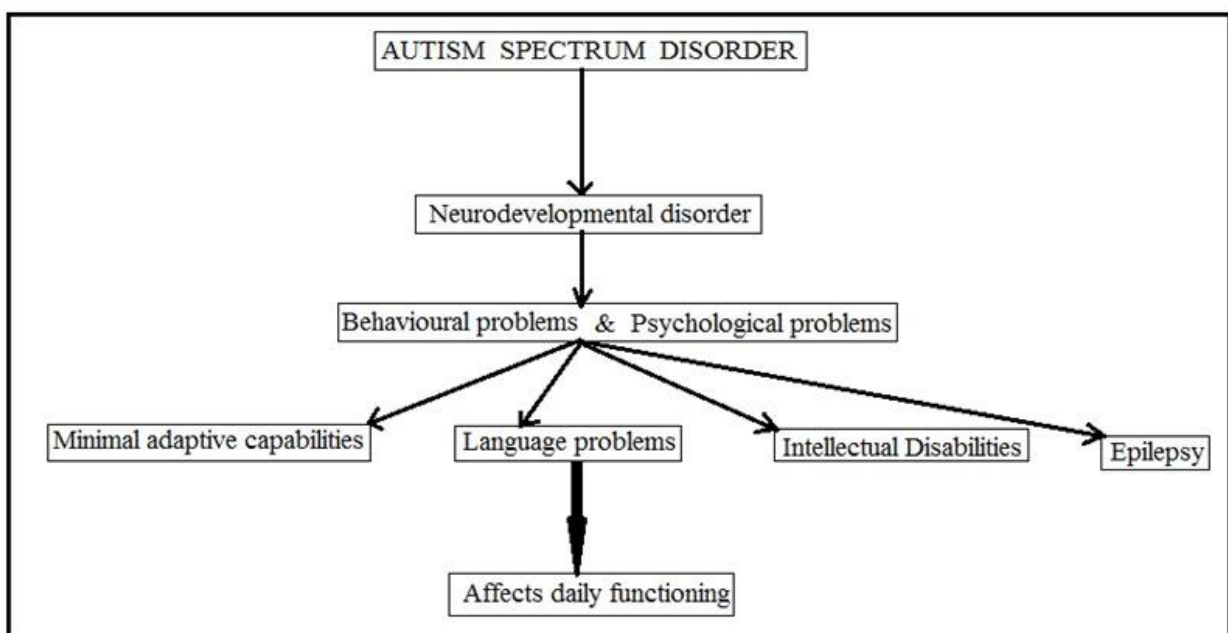
Falsify body language

- Extraordinary sensitive to light, sound or touch, pain or temperature.
- Prefers in eating only a few foods.

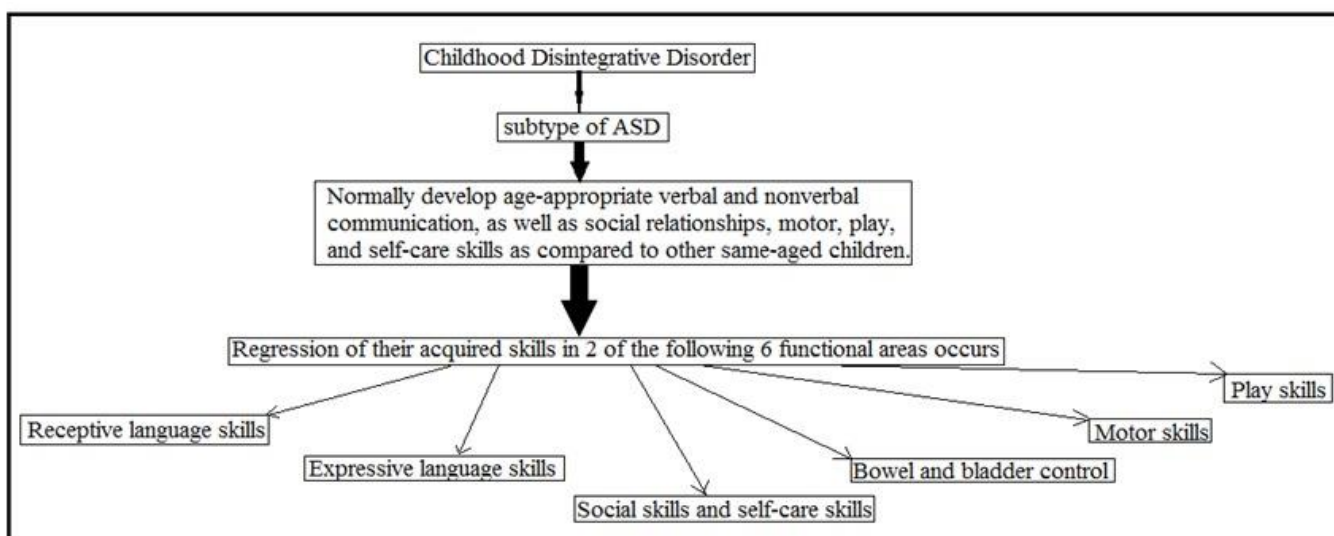


Autism spectrum disorders are not a disease, but their symptoms can be dealt with if there is an early diagnosis and a holistic approach

Awareness now needs to be focused on the right approach, says Mumbai-based developmental pediatrician, Samir Dalwai. “Everyone has been talking about spreading awareness,” Dr. Dalwai says, “but an important aspect is often missed out: that of reaching the right professional.”



They may present some unusual behavior like hand flapping, rocking and biting. They have trouble processing what they hear, see, touch or taste.



Children on the autism spectrum who have been part of early intervention programs have shown remarkable progress

India's first bridgital autism support network set up

- A different mind is a gifted mind', India's first bridgital autism support network. In a statement, Tata Sons Chairman N. Chandrasekaran said: "I congratulate Tata Power and CADRRE for launching the first-of-its-kind autism support network. As a responsible corporate group, we are committed to enabling equitable and balanced growth of the economy and society at large. The vision is to facilitate bridgital connectivity and social infrastructure with better access for all – including differently-abled and rural communities." (22).

What percent of autism is linked to mitochondrial dysfunction?

It is estimated the prevalence of mitochondrial disease in ASD as 7.2% (11), a more recent controlled study in the Journal of the American Medical Association suggested that mitochondrial dysfunction may be present in up to **80%** of children with ASD.

Males more susceptible to autism--

Autism Spectrum Disorder (ASD) affects 1 in 100 children in India. But the exact set of causes of autism remains unknown, and there is no cure for this disorder. However, the study

by researchers at the Central University of Kerala, found males can be more susceptible to Autism-like behavior than females when exposed to heavy metals like Lead. The study, published in the journal *Molecular Neurobiology*, also proposed that autism in children could be ameliorated by antioxidant therapy.23).

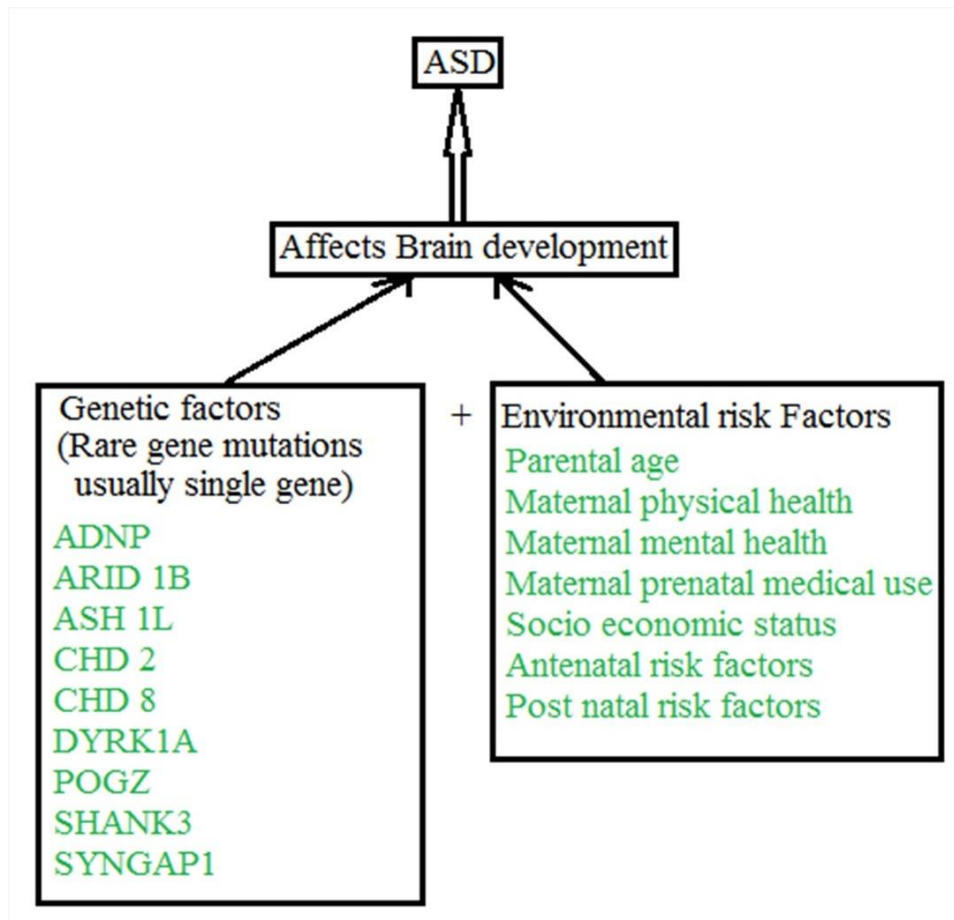
Effects on brain development

Autism-specific brain imaging features have been identified as early as 6 months of age, and age-specific brain and behavior changes have been demonstrated across the first 2 years of life, highlighting the developmental nature of ASD. New findings demonstrate that early brain imaging in the first year of life holds great promise for the presymptomatic prediction of ASD.

More than 1,000 genes are interconnected with ASD. Gene variations affect the risk of developing ASD. Most of the gene variations have a small effect. Genetic elements are appraised to contribute 50 to 70 percent of ASD risk.

The risk from gene variants, environmental factors, and birth complications, resolves an individual's risk of developing.

In addition to ASD and intellectual disability, this condition involves distinctive facial features and a wide variety of other signs and symptoms. Some of the other genes in which rare mutations are associated with ASD, often with other signs and symptoms, are *ARID1B*, *ASH1L*, *CHD2*, *CHD8*, *DYRK1A*, *POGZ*, *SHANK3*, and *SYNGAP1*.



We need to talk about autism

Research suggests that sleep disturbances — fragmented and erratic sleeping, frequent and prolonged night waking — impact over 80 percent of children with autism. It can exacerbate problem behaviors leading to a litany of complaints from the school or worse still, the exclusion of the child. (24)

Diagnostic and statistical manual of mental disorders (DSM)

Dr. DilipJeste, released the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) on May 18, 2013 (25).

DSM 5 indeed is a manual of the state of knowledge of the mental disorders, by experts in the field of mental health and related professions (26).

Autism Spectrum Disorder-----5 Red Flags

- They Don't Respond to Their Name. In general, babies learn to recognize their name and will acknowledge it by turning their head or with some other obvious gesture. ...

- They Don't Imitate Behavior. ...
- They Display Less Emotion. ...
- They Don't Engage in Joint Attention. ...
- They Pretend Less.
- Can a child with mild autism lead a normal life?
- The simple answer to this question is **yes, a person with autism spectrum disorder can live**

Screen time, a risk factor for autism spectrum disorder in early childhood

Screen time of 2-3 hours at one year of age predisposes boys to autism spectrum disorder at 3 years of age, according to a multicenter Japanese study reported in JAMA Pediatrics.¹

Researchers investigated the association of screen time at one year of age with the development of autism spectrum disorder at 3 years of age. (27)

Compared to girls, boys were thrice more likely to develop autism spectrum disorder and the association was stronger as the number of hours of screen time increased. No such association between autism spectrum disorder and screen time was noted for girls. (28)

Treatment

Treatment of ASD is complex, mainstay of the treatment is Behavioural but in those with challenging behaviours and co-occurring conditions like intellectual disability, medical, and mental health diagnoses pharmacological therapy is considered.

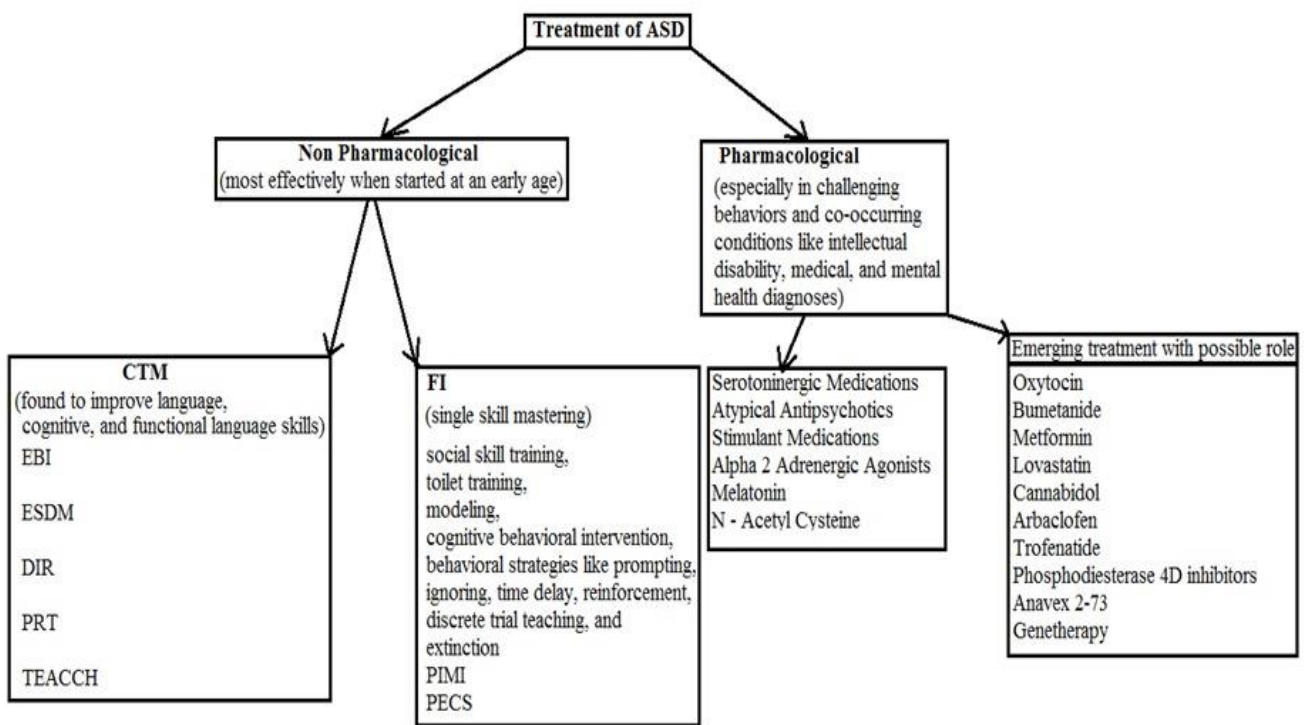
1. Non-pharmacological (Behavioural) interventions

Its most effective when started at an early age and the majority cater to young children to optimize their development and learning skills. Also have role in older children, adolescents, and adults. Main targets of these interventions in older individuals include changes in social, vocational, leisure skills, and independent living. The socio-cultural beliefs and economic capability of the family also moderate treatment impact and outcomes. Behavioral interventions are classified into two subgroups: comprehensive treatment models (CTMs) and focused interventions (FI) by Odem et al. and Wong et al.

a. Comprehensive treatment models (CTMs)

Instructions can be provided by instructors or by parents in naturalistic environments like home or in a classroom setting, individually or in a group, mainly focused on core ASD symptoms. Found to improve language, cognitive and functional language skills in young children, using intensive and long-term multi-disciplinary strategies.

Early behavioral interventions (EIBI), Early Start Denver model (ESDM), Developmental, Individual difference, relationship-based model (DIR/Floortime, or Greenspan model), Pivotal Response Training (PRT), Treatment and education of autistic and related communication handicapped children (TEACCH) are examples of CTMs.



b. Focused Interventions

Focused on a single skill or a specific area of developmental domain implemented as a structured session or in a naturalistic setting at home, school, clinic, or community settings, with peers or parents, and have behavioral, developmental, or educational purposes. This is provided for a short time, until the skill is mastered. Usually done for socially inappropriate and life-threatening behaviours that require rapid addressing.

Examples of Focused intervention includes social skill training, toilet training, modeling, cognitive-behavioral intervention, and behavioral strategies like prompting, ignoring, time delay, reinforcement, discrete trial teaching, and extinction. other examples are Peer-mediated Instruction and Intervention (PMII), also known as “Peer Modeling,” “Peer Initiation Training,” “Peer support” (29,30), and Picture Exchange Communication System (PECS) (31).

2. Pharmacological Treatments

They include Psychotropic medications, the use of these medications have markedly increased over the last decades especially in those with challenging behaviors and co-occurring conditions like intellectual disability, medical, and mental health diagnoses.

Mandell et al. reported that at least one psychotropic medication was prescribed in 56% of ASDs and three or more were prescribed in 20% (32).

Approximately 70% of autistic individuals showed Co-occurring mental health conditions including attention deficit and hyperactivity disorder (ADHD), irritability, aggression, mood, and anxiety issues (33,34,35).

General Principles

Always a high level of clinical suspicion for co-occurring mental health conditions is required for children and adolescents with communication challenges.

Managing clinicians should obtain information from the child when possible, family, and other providers including teachers and therapists.

Environmental changes and lack of skills can be the source of undesired behaviors and should be considered in the plan of care.

Pharmacological interventions are sometimes indicated and may facilitate their participation in therapy and enhance their daily functioning.

The principles used for psychopharmacological management are the same for children with ASD as for those with typical development.

Obtaining objective symptom measures from different sources before and after the intervention is key to objectively evaluating the response of treatment in different settings (36).

a. Serotonergic Medications

These are the most commonly prescribed medications for autistic individuals to treat anxiety, mood issues, and irritability. Symptoms in autistic individuals ranging from repetitive behaviors to anxiety is due to serotonin dysregulation. (37).

ASD should be analyzed genetically to diagnose associated Fragile X syndrome as studies with sertraline showed wonderful outcomes in Fragile X syndrome when compared to placebo.

Low dose sertraline treatment in children with FXS (12 to 50 months demonstrated improvement in the trajectory of both receptive and expressive language measures on the Mullen Scales of Early Learning (38).

a controlled trial for 6 months in children ages 2 to 6 with FXS (60% also had ASD) treated clinically with low dose sertraline (2.5 to 5.0 mg/day) and placebo (39).

In the children with both FXS and ASD, there was also a significant improvement on the Expressive Language subscale compared to placebo (40).

Low-dose sertraline did not demonstrate a benefit of sertraline compared to placebo.

In Idiopathic ASD (without FXS) in a study in young children ages 2 to 6 years.

b. Atypical Antipsychotics

FDA approved risperidone for children older than 5 years of age (41) and aripiprazole, approved for children 6 to 17 years of age (42).

For the treatment of irritability in ASD. Some benefit in repetitive behavior patterns was also noted.

The most common side effects include fatigue, increased appetite, GI symptoms, hyperprolactinemia, weight gain, and sedation, and less commonly activation including restlessness and akathisia. Thus, close clinical and laboratory monitoring is recommended because of adverse events associated with the same. They are also linked to more serious side

effects including dyslipidemia, hyperglycemia, metabolic syndrome, and extrapyramidal symptoms or drug-induced movement disorders.

Re-evaluation of treatment continuation should be done at regular intervals. Given that the efficacy and safety of these medications have not been established for the long-term treatment of irritability in autistic individuals.

c. Stimulant Medications

These are usually the first line of treatment to treat co-occurring attention deficit and hyperactivity disorder (ADHD). Almost half of autistic children meets the criteria for ADHD (43).

Treating co-occurring ADHD symptoms in autistic individuals should focus on improvement in enhancing their daily function in multiple settings, including learning, and hopefully, long-term functional outcomes improving associated symptoms causing impairment in the academic setting, peer relationships, and emotional regulation, which are also key predictors and mediators of functional difficulties in adulthood.

There are two main stimulant families: amphetamines and methylphenidate derivatives. Amphetamines slightly more efficacious and are usually better tolerated (44).

d. Alpha-2-adrenergic Agonists

Guanfacine and clonidine are used under this category. Alpha 2 agonists improve core ADHD symptoms and are frequently used in children below 5 years with ADHD or hyperarousal, cases with poor response to stimulants medications, or SNRI s, have unacceptable side effects, or have significant co-occurring conditions (i.e., sleep issues). The most common side effects of guanfacine include sedation, constipation, irritability, and aggression. (45, 46).

Study showed decreased irritability, stereotypy, hyperactivity, inappropriate speech, and hyperarousal behaviours with Clonidine (47).

e. Melatonin

. Studies suggested that low melatonin levels affect the circadian rhythm in autistic children (48).

Clinicians may recommend the use of melatonin which is usually well-tolerated and has a low incidence of side effects (49).

f. N-acetylcysteine

It can improve the imbalance of excitation: inhibition (E:I) that is seen in some forms of ASD (50).

Cysteine is also oxidized to cystine, which further helps to reduce glutamatergic neurotransmission.

A controlled trial showed significant improvement in irritability, stereotypic behaviours, SRS mannerisms were noted with NAC compared to Placebo. (51).

NAC was well tolerated although an occasional patient did not like the taste or had minimal gastrointestinal side effects.

g. Dietary Supplements

Sulforaphane is an antioxidant, anti-inflammatory, and mitochondrial protective agent. (53)

Vitamin D and omega 3 also showed significant improvement in irritability component compared to placebo in a study. (54)

REFERENCES

1. Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. *Pediatrics*. 2006; 118:e139–50.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington: American Psychiatric Publishing, 2013.
3. Halfon N, Kuo AA. What DSM-5 could mean to children with autism and their families. *JAMA Pediatr* 2013; 167:608-13. 10.1001/jamapediatrics.2013.2188
4. Maenner MJ, Rice CE, Arneson CL, et al. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. *JAMA Psychiatry* 2014; 71:292-300. 10.1001/jamapsychiatry.2013.3893
5. Kulage KM, Smaldone AM, Cohn EG. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *J Autism Dev Disord* 2014; 44:1918-32. 10.1007/s10803-014-2065-2
6. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR SurveillSumm* 2018; 67:1-23. 10.15585/mmwr.ss6706a1.
7. Yaylaci F, Miral S. A comparison of DSM-IV-TR and DSM-5 diagnostic classifications in the clinical diagnosis of autistic spectrum disorder. *J Autism Dev Disord* 2017; 47:101-9. 10.1007.
8. Kimhi, Y. (2014). Theory of mind abilities and deficits in autism spectrum disorders. *Top. Lang. Disord*. 34, 329–343.
9. Senju, A. (2013). Atypical development of spontaneous social cognition in autism spectrum disorders. *Brain Dev*. 35, 96–101.

10. McAdams D.P., Olson B.D. Personality Development: Continuity and change over the life course. *Annu. Rev. Psychol.* 2010; **61**:517–542. doi: 10.1146/annurev.psych.093008.100507.
11. Widiger T.A., De Clercq B., De Fruyt F. Childhood antecedents of personality disorder: An alternative perspective. *Dev. Psychopathol.* 2009; **21**:771–791. doi: 10.1017/S095457940900042X.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, DSM IV-R.* American Psychiatric Publishing; Washington, DC, USA: 2000.
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. American Psychiatric Publishing; Arlington, VA, USA: 2013
14. De Clercq B., DeFruyt F. A five factor model framework for understanding childhood personality disorder antecedents. *J. Personal.* 2012; **80**:1533–1563.
15. Edmonds G.W., Goldberg L.R., Hampson S.E., Barckley M. Personality stability from childhood to midlife: Relating teachers' assessments in elementary school to observer and self-relating 40 years later. *J. Res. Personal.* 2013; **47**:505–513.
16. Kuhn R (September 2004). "Eugen Bleuler's concepts of psychopathology". *History of Psychiatry.* **15** (59 Pt 3): 361–366.
17. Wolff S (August 2004). "The history of autism". *European Child & Adolescent Psychiatry.* **13** (4): 201–208
18. Manouilenko I, Bejerot S (August 2015). "Sukhareva--Prior to Asperger and Kanner". *Nordic Journal of Psychiatry (Report)* (published 31 March 2015). **69** (6): 479–482.
19. Wolff S (August 2004). "The history of autism". *European Child & Adolescent Psychiatry.* **13** (4): 201–208.
20. Happé F, Ronald A, Plomin R (October 2006). "Time to give up on a single explanation for autism". *Nature Neuroscience.* **9** (10): 1218–1220.
21. Lyons V, Fitzgerald M (November 2007). "Asperger (1906-1980) and Kanner (1894-1981), the two pioneers of autism". *Journal of Autism and Developmental Disorders.* **37** (10): 2022–2023.
22. Alok Deshpande, *The Hindu*, April/30/2022.
23. C P Sajit, Males more susceptible to autism: CUK study, *The Hindu*/Nov/09/2021.
24. Rashmi Das, We need to talk about autism, *The Indian Express*, June/2022.
25. 5th ed. Arlington: American Psychiatric Association; 2013. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders.*
26. Vihang N. Vahia, *Diagnostic and statistical manual of mental disorders 5: A quick glance*, *Indian J Psychiatry.* 2013 Jul-Sep; **55**(3): 220–223,
27. Dr Swati Y Bhave, Adjunct Professor in Adolescent Medicine; Dr D Y Patil Medical College, & Dr D Y Patil Vidyapeeth, Pune; Sr. consultant, Adolescent Pediatrics & Head-In-charge of Adolescent Wellness Clinic, Jehangir Hospital Pune, 01 June 2022
28. Kushima M, et al; Japan Environment and Children's Study Group. Association between screen time exposure in children at 1 year of age and autism spectrum disorder at 3 years of age: The Japan Environment and Childrens Study. *JAMA Pediatr.* 2022 Apr 1; **176**(4):384-391. doi: 10.1001/jamapediatrics.2021.5778.
29. Hume K, Steinbrenner JR, Odom SL, Morin KL, Nowell SW, Tomaszewski B, et al. Evidence-based practices for children, youth, and young adults with autism: third generation review. *Journal of Autism and Developmental Disorders.* 2021:1–20.
30. Hall T, Stegila A. Peer mediated instruction and intervention. Wakefield, MA: National Center on Accessing the General Curriculum Retrieved February. 2003; 8:2007.
31. Bondy AS, Frost LA. The picture exchange communication system. *Focus on autistic behavior.* 1994; **9**(3):1–19.
32. Mandell DS, Morales KH, Marcus SC, Stahmer AC, Doshi J, Polsky DE. Psychotropic medication use among Medicaid-enrolled children with autism spectrum disorders. *Pediatrics.* 2008; **121**(3):e441–e448
33. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry.* 2008; **47**(8):921–929.
34. Feroe AG, Uppal N, Gutiérrez-Sacristán A, Mousavi S, Greenspun P, Surati R, et al. Medication use in the management of comorbidities among individuals with autism spectrum disorder from a large nationwide insurance database. *JAMA Pediatr.* 2021; **175**(9):957–965

35. 7. Levy SE, Giarelli E, Lee LC, Schieve LA, Kirby RS, Cunniff C, et al. Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. *Journal of developmental and behavioral pediatrics : JDBP*. 2010; 31(4):267–275
36. Aishworiya, R., Valica, T., Hagerman, R., & Restrepo, B. (2022). An Update on Psychopharmacological Treatment of Autism Spectrum Disorder. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*, 19(1), 248–262.
37. Jansson L, Louhivuori L, Wigren H-K, Nordström T, Louhivuori V, Castrén M, et al. Brain-derived neurotrophic factor increases the motility of a particular N-methyl-D-aspartate/GABA-responsive subset of neural progenitor cells. *Neuroscience*. 2012; 224:223–234. doi: 10.1016/j.neuroscience.2012.08.038
38. Indah Winarni T, Chonchaiya W, Adams E, Au J, Mu Y, Rivera SM, et al. Sertraline may improve language developmental trajectory in young children with fragile x syndrome: a retrospective chart review. *Autism research and treatment*. 2012; 2012.
39. Hess LG, Fitzpatrick SE, Nguyen DV, Chen Y, Gaul KN, Schneider A, et al. A randomized, double-blind, placebo-controlled trial of low-dose sertraline in young children with fragile X syndrome. *Journal of developmental and behavioral pediatrics: JDBP*. 2016;37(8):619]
40. Potter LA, Scholze DA, Biag HMB, Schneider A, Chen Y, Nguyen DV, et al. A randomized controlled trial of sertraline in young children with autism spectrum disorder. *Front Psych*. 2019; 10:810
41. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002; 347(5):314–321
42. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009; 124(6):1533–1540
43. Salazar F, Baird G, Chandler S, Tseng E, O'sullivan T, Howlin P, et al. Co-occurring psychiatric disorders in preschool and elementary school-aged children with autism spectrum disorder. *J Autism Dev Disord*. 2015; 45(8):2283–2294.
44. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*. 2018; 5(9):727–738
45. 17. Scahill L, Aman MG, McDougle CJ, McCracken JT, Tierney E, Dziura J, et al. A prospective open trial of guanfacine in children with pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2006; 16(5):589–598.
46. Posey DJ, Puntney JI, Sasher TM, Kem DL, McDougle CJ. Guanfacine treatment of hyperactivity and inattention in pervasive developmental disorders: a retrospective analysis of 80 cases. *J Child Adolesc Psychopharmacol*. 2004; 14(2):233–241. doi: 10.1089/1044546041649084.
47. Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *J Clin Psychiatry*. 1992; 53(3):77–82.
48. Carmassi C, Palagini L, Caruso D, Masci I, Nobili L, Vita A, et al. Systematic review of sleep disturbances and circadian sleep desynchronization in autism spectrum disorder: toward an integrative model of a self-reinforcing loop. *Front Psych*. 2019; 10:366
49. Buckley AW, Hirtz D, Oskoui M, Armstrong MJ, Batra A, Bridgemohan C, et al. Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2020; 94(9):392–404.)
50. Rubenstein J, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav*. 2003;2(5):255–267. doi: 10.1034/j.1601-183X.2003.00037.x.
51. Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzberg LA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. *Biol Psychiatry*. 2012; 71(11):956–961. doi: 10.1016/j.biopsych.2012.01.014
52. Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, et al. Sulforaphane treatment of autism spectrum disorder (ASD) *Proc Natl Acad Sci*. 2014;111(43):15550–15555. doi: 10.1073/pnas.141694011153.
53. Zimmerman AW, Singh K, Connors SL, Liu H, Panjwani AA, Lee L-C, et al. Randomized controlled trial of sulforaphane and metabolite discovery in children with Autism Spectrum Disorder. *Molecular autism*. 2021; 12(1):1–22. doi: 10.1186/s13229-020-00405-7.

54. Mazahery H, Conlon CA, Beck KL, Mugridge O, Kruger MC, Stonehouse W, et al. A randomised controlled trial of vitamin D and omega-3 long chain polyunsaturated fatty acids in the treatment of irritability and hyperactivity among children with autism spectrum disorder. *J Steroid Biochem Mol Biol.* 2019; 187:9–16. doi: 10.1016/j.jsbmb.2018.10.017.

