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BEHAVIORAL Disorders in CHILDREN

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Chapter 3

Management of Autism Spectrum Disorder

Kaushik Ragunathan, Richa Tiwari, Gautam Kamila, Sheffali Gulati

INTRODUCTION

Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental condition characterized by difficulties in social communication and behavioral patterns. Emerging in early childhood, ASD affects individuals differently, ranging from mild difficulties to profound impairments in cognitive and emotional processing. Core deficits include repetitive behaviors, restricted interests, and impairments in social communication and interaction.[1] Early diagnosis and intervention are crucial in promoting positive outcomes and fostering a supportive environment for those living with ASD.

Presently, there is no known cure for ASD, but timely intervention can help. The goal of treatment is to maximize the child's functioning and improve their social, communication, functional, and behavioral skills. Nonpharmacological interventions continue to be the mainstay of therapy. Pharmacological agents are not curative but when used with nonpharmacological approaches improve core symptoms and may also help to reduce few associated comorbidities.

Role of complementary and alternative medicine (CAM), newer technologies, such as augmentative and alternative communication (AAC), artificial intelligence (AI) including deep learning models, virtual reality, and robotics, noninvasive neuromodulation, such as direct current stimulation (DCS) and transcranial magnetic stimulation (TMS) in management of ASD seems promising but needs further exploration.

NONPHARMACOLOGICAL MANAGEMENT IN AUTISM SPECTRUM DISORDER

Autism spectrum disorder management is not a one-size-fits-all approach and each person presents with unique strengths, weaknesses, and challenges. By acknowledging the distinct characteristics of each child, interventions can be tailored to optimize their potential and result in the most favorable functional outcomes **(Fig. 1)**. Families and caregivers should work closely with specialists and educators to adapt interventions to specific needs of the child.[2,3]

Autism spectrum disorder necessitates a personalized, multidisciplinary management strategy, targeting

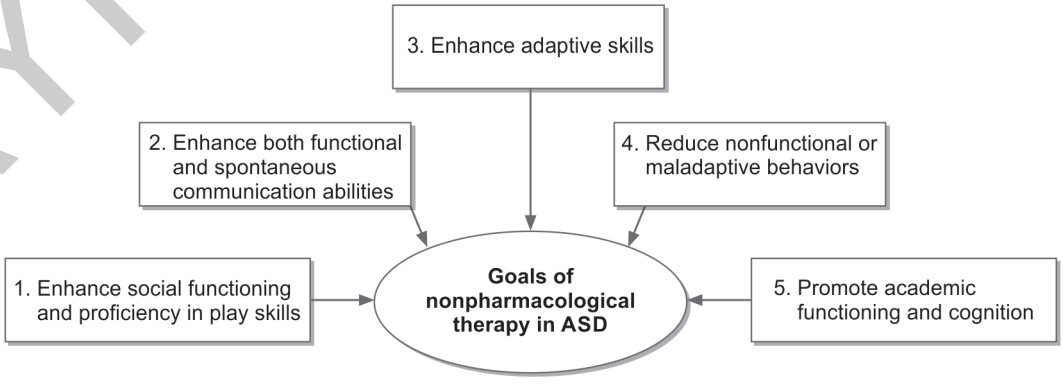


Fig. 1: Goals of nonpharmacological therapy in autism spectrum disorder (ASD).

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social, communication, and adaptive skill enhancement while reducing negative behaviors. Early intervention, capitalizing on individual strengths, and engaging caregivers are crucial for success. Tailored evidence-based therapies, such as applied behavior analysis (ABA) and speech therapy, ensure optimal progress. Regular assessments monitor development and guide necessary adjustments, aiming to maximize functioning and foster independence for each child. Collaboration among professionals, educators, and parents ensures a comprehensive approach to child's specific needs, ultimately improving their quality of life **(Table 1)**.[4]

Prompt diagnosis and immediate and intensive treatment have the capacity to significantly influence outcomes, especially in terms of behavior, functional abilities, and communication. While a cure remains elusive, over time, symptoms have the potential to ameliorate, and in a few instances, may reduce to the extent that they no longer result in impairment. The body of evidence supporting effectiveness of early intervention is growing, highlighting the importance of initiating interventions as soon as possible. Therapies can be administered through early intervention programs. As the child becomes older, school-based special education programs have a more prominent role in providing therapy.[4]

Treatment modalities that are used are summarized in **Figure 2** and include:[5]

Behavioral Approaches

Behavioral strategies have the most evidence in improving ASD symptoms. They center on modifying behaviors by comprehending antecedents and consequences of a particular behavior. These include ABA. ABA promotes favorable behaviors while discouraging undesirable ones, aiming to enhance a range of skills. The process involves monitoring and assessing progress. Various types of ABA can be used as per problem at hand. Most prominently used approaches are described here:

- *Discrete trial training (DTT):* Utilizes incremental instructions to teach desired behavior or response. Lessons are deconstructed into their fundamental components, with positive reinforcement for desired outcomes and behaviors, while undesired responses are discouraged.
- *Pivotal response training (PRT):* It takes place in a natural setting rather than a clinic setting. The goal of

TABLE 1: Key points to consider in planning individualized management of autism spectrum disorder (ASD).

Comprehensive assessment	To identify the individual's strengths, weaknesses, and specific needs, involving input from diverse professionals—psychologists, speech/occupational therapists, educators
Person-centered goals	Treatment plans must revolve around the individual's goals and aspirations, maximizing functional abilities and overall quality of life
Strength-based approach	Acknowledging and leveraging an individual's strengths enhances active engagement and motivation in therapy by capitalizing on their interests and abilities
Early intervention	Identifying and addressing challenges as early as possible for better progress and increased independence in the long run
Multidisciplinary collaboration	Holistic ASD management involves a multidisciplinary team of professionals including educators, therapists, physicians, and psychologists
Tailored therapies	Diverse evidence-based therapies including applied behavior analysis (ABA), speech therapy, occupational therapy, and social skills training tailored to the individual's unique needs and objectives
Communication support	Individuals with ASD benefit from augmentative and alternative communication (AAC) systems, aiding communication, and overcoming challenges in expression
Parent and caregiver involvement	Caregivers play a crucial role in implementing strategies at home and supporting the individual's progress beyond therapy sessions
Ongoing monitoring and adjustments	Consistent evaluation and progress monitoring are essential to ensure the ongoing effectiveness and relevance of the treatment plan, adapting it to the individual's evolving needs
Emphasis on independence	Integral to ASD management is fostering independence through life skills, empowering individuals for autonomy and confidence

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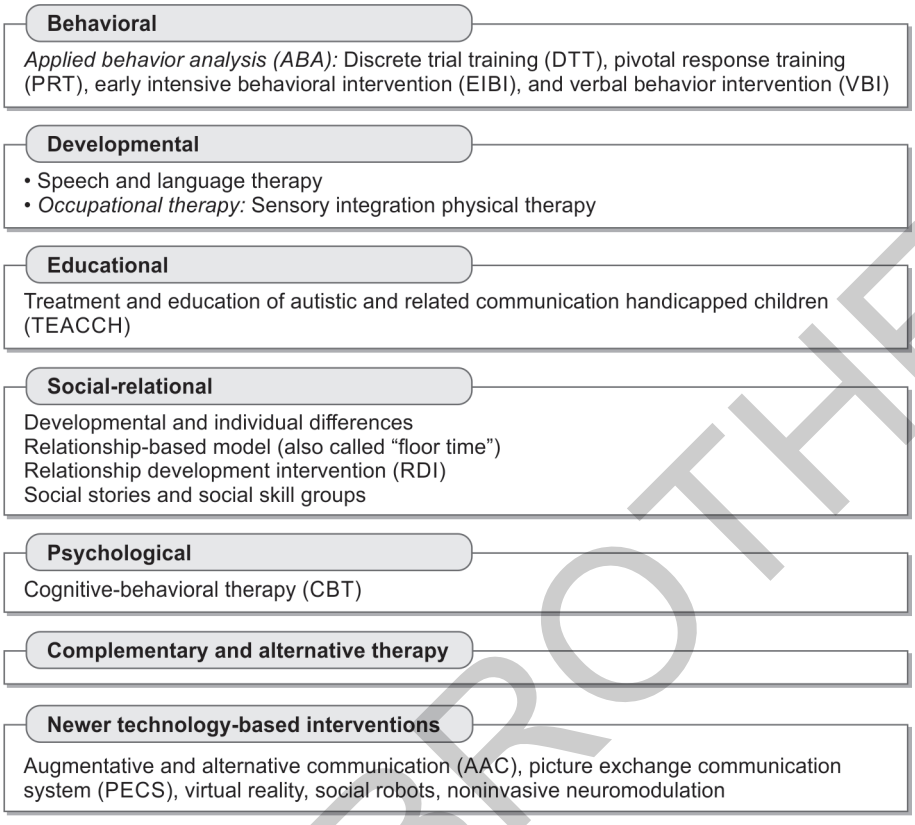


Fig. 2: Summary of nonpharmacological treatment approaches.[6,8,9]

PRT is to improve a few "pivotal skills" that will help the person learn many other skills. One example of a pivotal skill is to initiate communication with others.

- *Early intensive behavioral intervention (EIBI):* For children under age 5 years
- *Verbal behavior intervention (VBI)* focuses on language skills
- *Others:* Language paradigms and incidental teaching (teaching as events occur in the context of the natural environment).

Developmental Approaches

Developmental approaches aim to enhance distinct developmental skills like language or physical abilities as well as interconnected developmental capacities, and are often complemented by behavioral strategies. Common developmental therapies used in ASD are:

- *Speech and language therapy:* To enhance speech, language, and communication skills accommodating verbal, nonverbal, and alternative forms of expression in ASD such as signs/gestures/technology-assisted communication.
- *Occupational therapy:* It fosters independence by teaching skills, such as dressing, eating, bathing, and social interaction. It includes:
  - *Sensory integration therapy:* To address sensory challenges that may be restrictive or overwhelming.
  - *Physical therapy:* For enhancing motor skills. It includes motor training (including fine skills such as handwriting as well as gross motor training involving balance and posture).

The Early Start Denver Model (ESDM) is a broad developmental approach based on the principles of ABA. It is used with children 12–48 months of age.

Other developmental models are Social Communication, Emotional Regulation, and Transactional Support (SCERTS) program, and Joint Attention, Symbolic Play, Engagement and Regulation (JASPER). Parents and therapists employ play, social interactions, and shared focus within authentic environments to enhance language, social, and learning abilities.

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Educational Approaches

Structured educational programs with a team are given in a classroom setting. Intensive and individualized interventions during preschool years have shown positive results in many studies. These school curricula-based education programs with high staff-to-student ratio and specialized teachers create supportive and structured environments utilizing functional behavior analysis. Family involvement and close monitoring and transition planning are integral to the child's progress. These comprehensive interventions empower and optimize learning experiences and overall development of children with ASD. They help foster independence and social integration while addressing their unique challenges and strengths.

A notable type of educational approach is *Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH)*. It harnesses the consistency and visual learning capability of children with ASD, e.g., written/drawn daily routines in clear sight, boundaries around learning stations, and verbal instructions supplemented with visual instructions such as picture cards or physical demonstrations to aid learning objectives. Lessons are broken down into small steps, so they are easier.

Social-relational Approaches

Interventions center on enhancing social abilities and fostering emotional connections, often involving parental or peer mentor involvement.

- *Developmental, individual differences, and relationship-based model (also called "floor time"):* It promotes aligning with individual interests to broaden communication possibilities and nurturing emotional and intellectual development through skill acquisition.
- *Relationship development intervention (RDI):* It involves activities that increase motivation, interest, and abilities to participate in shared social interactions.
- *Social stories* provide simple descriptions of what to expect in a social situation.
- *Social skills groups* provide opportunities for people with ASD to practice social skills in a structured environment.

Psychological Approaches

Assist individuals with ASD in managing anxiety, depression, and mental health challenges. *Cognitive-behavioral therapy (CBT)* targets thought-behavior-emotion links. CBT enables collaborative goal setting and cognitive reframing for adaptive responses.

Complementary and Alternative Therapy

They comprise diverse practices beyond conventional medicine. Alternative therapies replace standard treatments, while complementary therapies supplement them. Integrative medicine combines both approaches with supportive evidence. CAM may merge into conventional practice with time as new and better evidence is generated. Families often explore CAM options alongside conventional therapies such as behavioral analysis in search for improvement. While CAM's allure in pursuit of a cure is strong, its efficacy varies **(Fig. 3)**. When discussing about CAM with family of child with ASD, maintain an open-minded and nonjudgmental stance. Inquire without presumptions understanding motivations behind choices suggested by them. Acknowledge and handle concerns about mainstream treatments and side effects, aim to be an ally and offer relevant resources.[6]

Technology-based Interventions and Supports

Augmentative and alternative communication, computer applications and software, and picture exchange communication system (PECS)—visual-based treatment that uses symbols instead of picture cards to enable communication, social robots, teleconferencing, video modeling, virtual reality [including virtual and three-dimensional (3D) environments to mimic social situations], and wearable sensors are all examples of the types of technology in this subcategory of publications.[7]

Increasing awareness of autism calls for essential interventions for toddlers, yet optimal strategies remain unclear. Limited ASD-specific interventions exist for those under 2 years old outside research settings. Integrative developmental behavioral models show effectiveness. Early intervention services, including speech and language interventions, are strongly recommended for toddlers with ASD. Emphasizing natural learning, sensorimotor exploration, communication development, and enriched environments is crucial. Limited research evaluates comprehensive programs for older ASD individuals, but ABA-based strategies show promise. Educational interventions for adolescents target social competence, emotional regulation, education, and independence skills.

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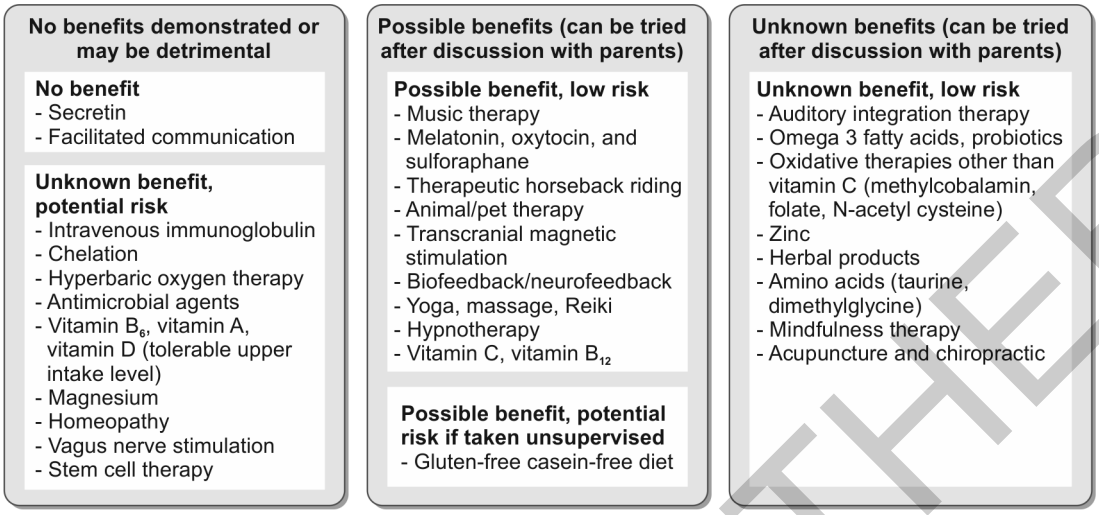


Fig. 3: Complementary and alternative therapy in autism spectrum disorder (ASD).
Source: Autism spectrum disorder in children and adolescents: Pharmacologic interventions. (2021) Available from: URL: https://www.uptodate.com/contents/autism-spectrum-disorder-in-children-and-adolescents-pharmacologic-interventions.

Transition care of a child with ASD needs utmost sensitivity and must be started early but gradually to allow time for adequate adjustments. Commencing transition planning at age 10 necessitates a collaborative approach with a multidisciplinary team responsible for the child's care, emphasizing the development of self-advocacy skills and ensuring parental comfort as key priorities.

ADDRESSING ASD RELATED COMORBIDITIES USING NONPHARMACOLOGICAL APPROACHES

Autism spectrum disorder is frequently associated with various comorbidities, often presenting unique challenges for affected individuals. Understanding these coexisting conditions are vital for providing comprehensive support.

Among these, comorbid conditions are intellectual disabilities, with approximately 40–50% of individuals with ASD experiencing coexisting cognitive impairments.

Additionally, attention-deficit/hyperactivity disorder (ADHD) is commonly observed, affecting about 30–60% of those with ASD.

Anxiety and depression are prevalent, affecting around 30–50% of individuals, as are motor coordination difficulties and language disorders.

Gastrointestinal (GI) issues, epilepsy, and sleep disturbances are also known comorbidities. Attending to these concerns can enhance focus, learning, and improve associated behaviors as well.

Sleep disturbances represent a common comorbidity in children with ASD, with prevalence ranging from 50 to 80%. A stepwise approach to sleep disturbances in children has been practiced even conventionally. This includes sleep education and implementation of healthy sleep practices followed by specific behavioral strategies. If nonsuccessful, medications can be cautiously titrated to the lowest effective dose for optimal treatment. The same principle applies to ASD. Parent-based sleep education has shown effectiveness in the general pediatric population and some children with ASD. Behavioral interventions, such as complete extinction (removing reinforcement to decrease a behavior) or graduated extinction and scheduled awakenings, are commonly used and have positive effects on various sleep problems. Other interventions, such as weighted blankets and aromatherapy, have limited evidence. Physical activity and yoga may also impact sleep in ASD children, but the findings are mixed. Massage has been found to induce improvements in sleep quality, diurnal behavior, and attention in children. Further research is needed for a comprehensive understanding of sleep interventions in this population.[9,10]

In conclusion, nonpharmacological therapies play a crucial role in the comprehensive management of ASD. These therapies offer a range of benefits, addressing core symptoms and improving the overall quality of life for individuals on the spectrum. Behavioral interventions, such as ABA, help enhance social skills, communication,

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and adaptive behaviors. Speech and language therapy aids in improving communication abilities, while occupational therapy supports the development of essential life skills and sensory integration. Additionally, social skill training fosters meaningful interactions and relationships. Sensory-based therapies promote coping mechanisms for sensory sensitivities. It is essential to recognize the individuality of each person with ASD, tailoring interventions to their unique needs and strengths. By embracing a holistic approach that incorporates these nonpharmacological therapies, we can create a more inclusive and supportive environment for individuals on the autism spectrum, empowering them to reach their fullest potential.

PHARMACOLOGICAL MANAGEMENT OF AUTISM SPECTRUM DISORDER

Principles of Pharmacotherapy in Autism Spectrum Disorder

The primary modality of treatment of ASD is nonpharmacological. There is no single medication that directly addresses the cognitive impairment in Autism. There are three approaches to plan pharmacotherapy in patients with ASD. The first and foremost measure is to target the core symptoms. Second is to address the comorbidities related to ASD. Third is still in its primitive stages of evidence which targets the basic underlying neurobiological processes related to syndromic autism (as in fragile X syndrome).[11]

However, over the last decade, there has been increasing evidence of polypharmacy in ASD ranging from 35 to 65%. It has been observed that the use of medications in autism increases with increasing age, associated intellectual disability (ID), and other psychological comorbidities.[4]

The initial assessment should include history and examination to rule out correctable medical factors that can cause/worsen the problem behavior in autistic children (e.g. gastroesophageal reflux and constipation that can worsen irritability and epilepsy that can add onto hyperactivity). The principles of initiating psychotropic medications in ASD are similar to that of any other typically developing child. However, the treating clinician should carefully weigh the risk-benefit ratio before doing so *because children with ASD are slightly more sensitive to adverse effects of these medications*. Hence, it should be started at a lower dose, gradually titrated to response at a very slower rate. The medication may be gradually tapered off when symptoms have been adequately controlled and have been taken care of by the non-pharmacological behavioral interventions.

PHARMACOLOGICAL TREATMENT OF CORE SYMPTOMS IN ASD

Repetitive Behaviors

Pharmacotherapy when used alone will not act on repetitive behaviors, which includes motor stereotypes, behavioral rigidity, and compulsions. But, it may be utilized as a part of comprehensive behavioral intervention for better results. Dopamine receptor blockers (atypical antipsychotics) may have some effect on repetitive behaviors. Studies suggest that short-term courses of aripiprazole or risperidone may show benefits in aggression and tantrum related to repetitive behaviors.[11]

The other medications that have been tried include antiseizure drugs (divalproex sodium and topiramate) and selective serotonin reuptake inhibitor (SSRI) (fluoxetine and fluvoxamine).

Impaired Communication and Reciprocal Social Interaction

There are no medications targeting social communication in ASD. However, treating comorbidities can result in some improvement in this domain.

PHARMACOLOGICAL TREATMENT OF COMORBIDITIES RELATED TO ASD

Hyperactivity, Impulsivity, and Inattention

Hyperactivity and inattention are one of the most common presenting core symptoms in ASD. Stepwise management has been suggested in children. During the first visit, a thorough baseline behavioral assessment is done and targeted interventions are advised. After a period of 3–6 months, the child is again assessed for the same and if there is no response, a trial of pharmacotherapy can be initiated. This is undertaken on the basis that children with ASD are more sensitive to psychostimulant doses and especially those with ID and other comorbidities may not respond well to medicines.[4]

The first-line medication is usually a stimulant medication (dextroamphetamine salts or methylphenidate) initiated in a low dose. The dose is gradually titrated for response. In case of adverse effects or no response to the first-line medications, a trial of selective norepinephrine

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reuptake inhibitor (SNRI) (atomoxetine) may be given. The other options include α-adrenergic agonists (guanfacine and clonidine) and atypical antipsychotics (aripiprazole and risperidone).

Irritability and Disruptive Behaviors

The United States Food and Drug Administration (USFDA) has approved two medications for irritability in autism. *Risperidone*, a second-generation atypical antipsychotic (D2 receptor antagonist), was approved in 2006 for irritability, aggression, tantrums, and deliberate self-injury in patients >5 years of age. *Aripiprazole* was approved in 2009 by FDA for children and adolescents of age 6–17 years. These two medications have an affinity for dopamine, serotonin, histaminergic, and α-adrenergic receptors in the brain. The treating clinician should keep a watch for weight gain and sedation. The other medicines of this family, olanzapine and quetiapine, are not FDA approved and lack sufficient evidence for routine use in children.[11]

Few other medications for irritability include α-2 adrenergic agonists (clonidine and guanfacine), SSRIs (fluvoxamine and citalopram), antiseizure medications (ASMs) (valproic acid and divalproex sodium), and SNRI (venlafaxine). These drugs are commonly used off-label for irritability but lack sufficient evidence to be used as the first-line agent.

Minocycline has been tried in ASD with fragile X syndrome. Arbaclofen has been studied in smaller patient groups. Amantadine [noncompetitive N-methyl-D-aspartate (NMDA) antagonist] has yielded positive effects in irritability and hyperactivity. However, we need blinded randomized controlled trials (RCTs) with large sample size before a recommendation can be made for these three drugs.

Anxiety and Depression

The anxiety disorders amenable to pharmacotherapy include social phobias, generalized anxiety disorder, and separation anxiety. The first-line treatment option for anxiety related to ASD is always CBT. Pharmacotherapy includes SSRI (fluoxetine, sertraline, escitalopram, and citalopram), α-agonists (guanfacine and clonidine), atypical antipsychotics, and β-blockers (propranolol). Short-acting benzodiazepine (lorazepam) has been tried for event-related anxiety. For mood-related disorders, starting on a mood stabilizer and/or a second-generation antipsychotic drug is recommended.

For depression, SSRIs are widely used in children. However, it has been noted that ASD children are more sensitive to adverse effects. Hence, it is recommended that they are started in a lower dose and very gradual titration to response may be tried. Particularly in adults, fluoxetine seems to be best tolerated among serotonergic agents.

Obsessive-Compulsive Disorder Related Disorders (OCD Related Disorders)

First-line therapy in obsessive-compulsive disorder (OCD) related disorders is CBT, although it may be less effective in children with ASD. A trial of SSRI may be given particularly if associated with anxiety or depression. Risperidone and clomipramine are alternative options.

Sleep Disorder

Children with ASD are well known to have sleep issues such as decreased sleep duration, increased sleep latency, and disturbed sleep. Studies suggest that low melatonin level in children with ASD is related to altered circadian rhythm. A low dose of oral melatonin supplement can be added along with behavioral intervention and sleep hygiene measures. The usual dose ranges from 1 to 6 mg. α-adrenergic agents (clonidine) and antihistamines (diphenhydramine) are being used off-label for insomnia, but there is insufficient evidence to support the same. Melatonin, when used along with CBT, shows better results.

Gastrointestinal and Feeding Issues

Common GI symptoms in children with ASD include constipation, vomiting, gastroesophageal reflux, abdominal pain, feeding issues, and diarrhea. The medical management is the same as that of any other typically developing child. But autistic children may benefit from consistent behaviorally informed interventions for encopresis and constipation.

Autistic children have feeding issues in the form of food selectivity, rumination, pica, and compulsive eating. This is usually related to their repetitive behavior. Feeding problems affect nutrition and can cause micro-/macronutrient deficiencies. The management is same as in any other typically developing child, but in addition targeted behavioral interventions on a case-to-case

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basis should be designed. If they fail, gastrostomy-tube placement and nonoral feeding should be tried.

Pica may be associated with the risk of iron deficiency, lead poisoning, ingestion of nonedible substances including bezoars leading to obstruction or intestinal perforation.

Seizures, Epilepsy, and EEG Abnormalities in ASD

In the following description, we have tried to arrive at a reasonable strategy to approach an autistic child with seizure and an autistic child with no seizure but with electroencephalogram (EEG) abnormalities.

Child with ASD and clinical seizure: Incidence of epilepsy is high in autistic patients as compared to typically developing children. The risk is even greater if there is an associated ID. The challenge is to rightly identify the clinical seizure, especially in those with complex motor stereotypes. Focal seizures with impaired awareness are the most common semiology, but generalized tonic, or tonic-clonic seizures may also occur. Autistic kids may have some complex stereotypes such as staring episodes or gaze deviation which may be mistaken as seizure. Video documentation of events and EEG documentation may help in deciding regarding initiation of ASM. The term, *interictal spike discharges,* is used to denote the occurrence of EEG abnormalities between seizures.

In syndromic causes of autism such as fragile X and tuberous sclerosis complex (TSC), there is a need for ASM therapy and dosage is optimized till clinical response. There are even specific choices of ASM like that in management of spasms in TSC with vigabatrin.

Subclinical electroencephalographic abnormalities (SEAs) or isolated epileptiform discharges (IEDs) are at times used interchangeably to indicate epileptiform discharges on EEG but complete absence of identifiable clinical seizures. Several studies have reported SEAs in the range of 4–86% in ASD even if no clinical seizures have been noted. The discharges were most frequently noted from the right temporal lobe or bilateral temporal region, which is usually implicated in social deficits and language dysfunction respectively. The presence of EEG abnormalities has been associated with lower IQ, impaired adaptive skills, marked increase in stereotypies and aggression.[12]

EEG Abnormalities in ASD: To Treat or Not to Treat?

The *first step* in approaching SEAs in autistic children is to look for the contributory role of these discharges in cognitive and behavioral abnormalities. In conditions such as electrical status epilepticus in sleep (ESES), where there may not be ongoing clinical seizures but high incidence of electrical discharges during sleep may contribute to cognitive regression and significant behavioral problems (hyperactivity, aggression, and irritability). The management differs from the rest of the epileptic conditions. Steroids (pulse methylprednisolone) and benzodiazepines are proven successful modalities in ESES. A similar condition is Landau–Kleffner syndrome where steroids are the first-line therapy. Lennox–Gastaut syndrome is distinct from the two above-mentioned conditions since it presents with multiple semiology of seizures and characteristic EEG findings.

After ruling out the above-mentioned conditions or direct contributory role of the EEG discharges to ASD, *the next step* is to make an individualized approach on a case-to-case basis. At present, there is insufficient evidence to support initiating ASM for treating epileptiform discharges in ASD even in autistic regression. However, it has been noted that there can be some tangential benefit in behavioral problems due to the mood stabilizing action of a few ASM.[13]

Choice of ASM: The most frequently used medications include valproate, levetiracetam, and lamotrigine. Valproate has a broad spectrum of action when used as an ASM and in addition has been well known for its mood stabilizing action. It has some role in improving aggression, irritability, and repetitive behavior in autistic cohorts. Lamotrigine has a very similar neuropsychiatric profile to valproate. These two medications (and carbamazepine) are used in instances where there are associated mood disorders or depression.[13]

The following medications are to be used with caution in those with cognitive impairment: phenobarbitone, topiramate, zonisamide, and phenytoin.[13]

The following medications should be used with caution in those with psychiatric/behavioral concerns: levetiracetam, phenobarbitone, zonisamide, phenytoin, topiramate, and perampanel.

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TABLE 2: Summary of common medications used in ASD.

Pharmacotherapy	*Symptoms targeted*	*Adverse effects*	*Comments*
Atypical antipsychotics: • Risperidone—D_2 receptor antagonist – Dose range (0.25–3.5 mg/day) – Doses up to 10 mg/day have been reported in literature for children >45 kg • Aripiprazole—D_2 receptor antagonist with partial agonist properties – Dose range (2.5 mg/day to a maximum of 15 mg/day has been tried)[14]	• Irritability • Disruptive traits	• Increased appetite, weight gain, sedation, fatigue, and drooling • Elevated prolactin levels and tremors • Start at a lower dose, very gradual titration, monitor for sedation, and extrapyramidal adverse effects • *Serious adverse effects:* Metabolic syndrome, dyslipidemia and hyperglycemia • Sedation (after risperidone) is likely to reduce after 8 weeks of therapy • As compared to risperidone, aripiprazole is noted to have less sedation and lower incidence of extrapyramidal symptoms	Risperidone and aripiprazole are *FDA-approved medications* targeting irritability in ASD[4]
α-*2 adrenergic agonists:* Clonidine and guanfacine	• Irritability • Hyperactivity	• Sedation and drowsiness • Fatigue • Constipation • Worsening of irritability and aggression • Appetite suppression, hypotension, and bradycardia	α-*2 agonists can be considered in:* • Children <5 years with ADHD symptoms, and hyperarousal • Failed response/intolerance to stimulant medications/SNRIs • Coexisting sleep issues[4]
Serotonergic medications: This category includes the SSRIs, SNRIs (serotonin-norepinephrine reuptake inhibitors), and tricyclic antidepressants	• Anxiety • OCD • Disruptive behaviors • Irritability • Mood disorders • Repetitive behaviors	Autistic children may be more sensitive to behavioral activation with SSRIs	Serotonin dysregulation has been reported in autism in relation to anxiety, depression symptoms, and repetitive behaviors
SSRIs: • Fluvoxamine • Clomipramine (5–10 mg/day) • Fluoxetine (5–20 mg/day) • Buspirone (2.5–5 mg/day) • Citalopram (2.5–20 mg/day)		These medications may cause activation, sedation, insomnia, diarrhea, dry skin, pruritus, and rarely worsening of stereotypies	• There is insufficient evidence to support SSRIs for core symptoms but may help in anxiety and depression symptoms • FDA has mentioned caution in children with ASD taking SSRI (especially fluoxetine) due to concerns regarding suicidal ideation in depressed children with ASD. So, these children should be carefully monitored
SNRIs (atomoxetine): Inhibit the presynaptic norepinephrine transporter	Hyperactivity (nonstimulant medication)		• Atomoxetine may be considered if failure/intolerance/no response to first-line stimulant medications • It is preferred in coexisting anxiety

Contd…

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Contd…

Pharmacotherapy	*Symptoms targeted*	*Adverse effects*	*Comments*
Psychostimulant medications: Methylphenidate, dexmethylphenidate, lisdexamfetamine, and dextroamphetamine	• Inattention • Hyperactivity • Impulsivity	• Insomnia and appetite suppression are well-known adverse effects • Worsening of irritability and depressive symptoms	In case of inattention/hyperactivity, a stepwise approach is usually implemented with regard to pharmacotherapy, as children may be more sensitive to adverse effects (as explained in the text)
Antiseizure medications: • Levetiracetam • Lamotrigine • Divalproex sodium • Bumetanide	• For indications, other than management of seizures • Mood stabilizing effects • Irritability • Repetitive behaviors		There have been constant discussions over the role of levetiracetam in worsening of behavioral problems, but till date there is no conclusive evidence to support the use as first-line ASM or to avoid levetiracetam in those with ASD

(ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder; FDA: Food and Drug Administration; OCD: obsessive-compulsive disorder; SSRIs: selective serotonin reuptake inhibitors)

DRUGS TARGETING NEUROBIOLOGICAL PROCESSES RELATED TO SYNDROMIC AUTISM (ROLE OF PRECISION MEDICINE)

The functional effect of tuberous sclerosis is related to activation of the mammalian target of rapamycin (mTOR) complex. There are several ongoing trials utilizing everolimus (mTOR inhibitor) as an adjunctive therapy in drug refractory epilepsy in TSC. The initial results are assuring.

SCN2A mutations have been related to ID and autism with or without epilepsy. There is a role for sodium channel blockers (phenytoin). PCDH19 (protocadherin-19)-related disorders are associated with drug refractory epilepsy with or without behavioral problems. PCDH19 is suspected to have a role in gamma-aminobutyric acid type A ($GABA_A$) function. Ganaxolone plays a role in $GABA_A$ function. Its role in epilepsy and neuropsychiatric problems is yet to be investigated.[13]

The other two common genetic associations in ASD are *SCN1A* and *MECP2*. Mutations in *SCN1A* are related to Dravet syndrome. Nonepilepsy phenotypes are associated with autistic traits. In *MECP2*-related Rett syndrome, hand stereotypies are a common autistic feature although these kids may have good social interaction.

NEWER TREATMENT STRATEGIES

After extensive review of the newer drugs/ongoing trials on pharmacotherapy in ASD, the authors felt that the following drugs are worth mentioning. The other treatment options have been listed in **Table 3**.

Oxytocin is a neurohypophyseal peptide synthesized in the hypothalamus and is actively related to the receptors in nucleus accumbens, amygdala and hippocampus that play a role in social behaviors. Several trials have shown benefit with intranasal/intravenous oxytocin in terms of short-term improvement in social communication. But, there is insufficient evidence to support its long-term use. Intranasal oxytocin has adverse effects such as nasal irritation, skin irritation, fatigue, and diarrhea.

Till date, there is no robust evidence to support probiotics for GI symptoms or behavioral problems in ASD. The existing blinded RCTs have found no significant difference in terms of GI symptoms/behavior. However, the studies regarding prebiotics are assuring. Especially the combination of prebiotics and exclusion diet (casein and gluten-free diet) has reduced GI symptoms and antisociability scores.

Cannabidiol is the nonpsychotropic component of marijuana, and has been tried in the management of motor deficits like the tremor in Parkinson's disease and in anxiety, pain, and nausea. The possible mechanisms implicated in ASD include $GABA_A$ agonist potentiation, stimulation of 5-HT1A receptors and possible role in mitochondrial function. Large-scale studies are required to support its use in children.

A newer therapeutic option, resveratrol, a plant phytoalexin has been tried in ASD for its anti-inflammatory

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TABLE 3: Newer/emerging treatment options in ASD.

Medication/supplement	*Possible mechanism of action*	*Comment*
Dietary supplements: Sulforaphane (in broccoli and many cruciferous vegetables) Omega-3 fatty acids	• Antioxidant • Anti-inflammatory • Mitochondrial protective agent	At present, the evidence to suggest the role of broccoli in improvement of core symptoms is still inconclusive
N-acetyl cysteine (NAC)	• Antioxidant action • NAC lowers glutaminergic transmission, thereby improving the imbalance between E:I (excitation:inhibition) ratio[15]	Initial studies have shown improvement in irritability and stereotypies
Metformin	• Role in specific subgroups of ASD (fragile X syndrome) • In the absence of FMRP, there is hyperactive insulin receptor, upregulation of mTORC1, MAPK/ERK pathways	• Specifically targets overeating in ASD (especially in fragile X syndrome, Prader–Willi syndrome) • Minor degrees of improvement in irritability and aggression
Oxytocin	Neuropeptide from hypothalamus with a critical role in social functioning	• Suggested role in improvement in social reciprocity, repetitive behaviors, and emotion recognition • Preliminary studies have shown some evidence of improvement in social cognition, although they require large RCTs
Phosphodiesterase-4D (PDE4D) inhibitors	cAMP level is downregulated in fragile X syndrome. PDE4D inhibitors cause inhibition of cAMP breakdown	Positive results in a small group of adult males with fragile X syndrome, in terms of cognition and behavior
Cannabidiol (CBD)	• Potentiation of $GABA_A$ agonist action • Stimulation of 5-HT1A receptors • Improves mitochondrial function	• Trials of oral and topical cannabidiol in ASD are ongoing • Role of CBD in drug refractory epilepsy such as Dravet and Lennox–Gastaut syndrome has been well established • However, there is no sufficient evidence at present to support its role in behavioral problems
Probiotics and prebiotics	Commonly tested options are: • *Bifidobacterium*, *Lactobacillus*, and *Lacticaseibacillus*-based probiotic preparations • They increase the production of microbial metabolites, such as short-chain fatty acids (SCFA) and many other anti-inflammatory cytokines	• Benefits of probiotics on core behavioral symptoms of ASD are not satisfactory based on the existing trials • However, prebiotic and symbiotic combinations have shown assuring results on trials. But at present there is no sufficient quality of evidence to provide recommendations for the same

(ASD: autism spectrum disorder; cAMP: cyclic adenosine monophosphate; ERK: extracellular signal-regulated kinase; FMRP: fragile X mental retardation protein; MAPK: mitogen-activated protein kinase; mTORC1: mTOR complex 1; RCTs: blinded randomized controlled trials)

and antioxidant properties. However, the existing RCTs have shown conflicting results between studies and hence require large-scale studies.

There are several ongoing studies worldwide with focus on newer neurobiological pathways and with a scope for precision medicine which may be the future of pharmacotherapy in autism.

CONCLUSION

The primary modality of treatment in ASD is non-pharmacological; drug therapy can be used as a bridge or on a short-term basis as a support to the behavioral interventions. Nonpharmacological approaches must be highly individualized. The choice of therapy approach and its delivery is a team effort with a common goal in view.

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Therapies must always be given by a well-trained professional in collaboration with other team members. Behavior, developmental, and integrative models of therapy should never be ignored while the child is started on medications. None of the existing medications target cognitive improvement in ASD; the medications are targeted predominantly toward comorbidities of ASD. Risperidone and Aripiprazole are FDA-approved medications targeting irritability (disruptive behaviors) in ASD. When pharmacotherapy is planned for an autistic patient, a detailed baseline cognitive and behavioral assessment should be documented by a qualified psychologist and should be repeated frequently to document response to the medication. At present, there definitely is no sufficient evidence for initiating ASM in a child with ASD with subclinical EEG abnormalities. The decision has to be taken on a case-to-case basis if the contributory role of the SEAs to the behavioral problems is proven.

REFERENCES

1. American Psychiatric Association (Eds). Diagnostic and statistical manual of mental disorders: DSM-5, 5th edition. Washington, DC: American Psychiatric Association; 2013. p. 947.
2. Narzisi A, Costanza C, Umberto B, Filippo M. Non-Pharmacological Treatments in Autism Spectrum Disorders: An Overview on Early Interventions for Pre-Schoolers. Curr Clin Pharmacol. 2014;9(1):17-26.
3. Myers SM. Management of autism spectrum disorders in primary care. Pediatr Ann. 2009;38(1):42-9.
4. Hyman SL, Levy SE, Myers SM; Council on Children with Disabilities, Section on Developmental and Behavioral Pediatrics. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. 2020;145(1):e20193447.
5. Nash K, Carter KJ. Treatment options for the management of pervasive developmental disorders. Int J Psychiatry Med. 2016;51(2):201-10.
6. Cheng A. (2019). Benefits of Nonpharmacological and Pharmacological Treatments in Autistic Children. [online] Available from: https://scholar.dominican.edu/nursing-senior-theses/21/ [Last accessed September, 2023].
7. Lecciso F, Levante A, Fabio RA, Caprì T, Leo M, Carcagnì P, et al. Emotional Expression in Children With ASD: A Pre-Study on a Two-Group Pre-Post-Test Design Comparing Robot-Based and Computer-Based Training. Front Psychol. 2021;12:678052.
8. Linden A, Best L, Elise F, Roberts D, Branagan A, Tay YBE, et al. Benefits and harms of interventions to improve anxiety, depression, and other mental health outcomes for autistic people: A systematic review and network meta-analysis of randomised controlled trials. Autism. 2023;27(1):7-30.
9. Keogh S, Bridle C, Siriwardena NA, Nadkarni A, Laparidou D, Durrant SJ, et al. Effectiveness of non-pharmacological interventions for insomnia in children with Autism Spectrum Disorder: A systematic review and meta-analysis. PLoS OnE. 2019;14(8):e0221428.
10. Esposito D, Belli A, Ferri R, Bruni O. Sleeping without Prescription: Management of Sleep Disorders in Children with Autism with Non-Pharmacological Interventions and Over-the-Counter Treatments. Brain Sci. 2020;10(7):441.
11. Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol. 2018;32(1):3-29.
12. Precenzano F, Parisi L, Lanzara V, Vetri L, Operto FF, Pastorino GMG, et al. Electroencephalographic Abnormalities in Autism Spectrum Disorder: Characteristics and Therapeutic Implications. Medicina (Kaunas). 2020;56(9):419.
13. Watkins LV, O'Dwyer M, Shankar R. A review of the pharmacotherapeutic considerations for managing epilepsy in people with autism. Expert Opin Pharmacother. 2022;23(7):841-51.
14. Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, et al. Swaiman's Pediatric Neurology: Principles and Practice, 6th edition. Edinburgh: Elsevier; 2018.
15. Aishworiya R, Valica T, Hagerman R, Restrepo B. An Update on Psychopharmacological Treatment of Autism Spectrum Disorder. Neurotherapeutics. 2022;19(1):248-62.

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BEHAVIORAL Disorders in CHILDREN

Behavioral disorders in children are on the rise over the last few years and it has been a relatively lesser known and practiced subject for general pediatricians.

This surge accentuates the pressing need for comprehensive understanding and proficiency in this domain. The present scholarly work delves deeply into the intricate fabric of behavioral issues afflicting children, meticulously authored by eminent academicians and clinicians. This book assumes paramount importance as a vital resource, equipping practicing pediatricians, as well as aspiring fellows and postgraduates, with the requisite knowledge to grasp and effectively apply behavioral insights within the clinical sphere, thus enhancing patient care and outcomes.

Key Points

- Internalizing behavioral disorders like autism spectrum disorders, attention-deficit hyperactivity disorder (ADHD), generalized anxiety disorders, phobia, and obsessive-compulsive disorders
- Externalizing behavioral disorders like aggressive behavior, oppositional defiant disorder, and habit disorders
- Genetics and pharmacology of behavioral disorders
- Mobile addiction and behavioral problems
- Cognitive behavioral therapy and counseling of parents and children.

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Printed in India

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ISBN 978-93-5696-858-5

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