

Strategic Management of Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is a complex, multi-factorial, neurodevelopmental disorder with a dynamic set of neuronal and behavioral abnormalities, which involves various systems of the body. A sharp rise in the incidence of ASD cases has been noted worldwide owing to the complex combination of increased awareness, broader diagnostic criteria, poor nutrition, various prenatal, perinatal and postnatal factors, genetic predisposition precipitated by adverse environmental conditions and gynecological interventions. ASD is not a single disorder but it encompasses a broad spectrum of disorders resulting from various genetic and non-genetic risk factors contributing independently as well as together. The co-occurrence of different disorders in ASD seems to be normal rather than the exception. Although no medicine has been recognized to treat ASD, several medicines have been proposed to ameliorate co-morbid conditions and are found to be the most efficacious in diminishing ASD-associated symptoms such as self-harm, aggressive episodes, irritability, unusual conduct, in-attention, anxiety, depression, hyperactivity and insomnia. Complementary therapies such as cognitive behavioral therapy, Speech therapy, music therapy, educational therapy, psychotherapy, occupational therapy and nutritional therapy have shown partial benefits when applied individually as per the specific needs of the child. Most importantly compassionate care coupled with assurance and reassurance by the parents and friends is crucial. No single therapy works completely for all kinds of patients. Different treatment approaches have been practiced to address different aspects of social behavior, communication deficits, physical disabilities, specific symptoms and co-morbidities. Therefore, designing appropriate routine and behavioral support by a psychotherapist tailored for each child as per its symptoms is essential for providing a comfortable life. Several substances targeting immune dysfunction, neuroinflammation, glutamate/GABA imbalance, NMDA receptors and neuropeptides are undergoing clinical trials with variable success. Stem cell therapy aimed at preventing neuro-degeneration, modulating the immune system and improving brain function is also being investigated. To help the unfortunate child and improve the quality of life of concerned families, an integrative approach combining drug therapy and non-drug therapy offers a great promise. However, along with the therapeutic management, the cooperation of family members backed by society is necessary for enhancing the quality of life of a child suffering from ASD.

Keywords: Autism; Drug Therapy; CBT; Nutrition; Strategic

Abbreviations

AAT: Animal-Assisted Therapy; ABA: Applied Behavior Analysis; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CBT: Cognitive Behavioral Therapy; DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth edition; FDA: Food and Drug Administration; GABA: γ -Aminobutyric Acid; GFCD: Gluten-Free Casein-Free Diet; HFD: High-Fat Diet; KD: Ketogenic Diet; NMDA: N-Methyl-D-Aspartate; SSRI: Selective Serotonin Reuptake Inhibitors

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Preamble

Autism spectrum disorder (ASD) is a complex; life-long neurodevelopmental disorder diagnosed in early childhood and characterized by symptoms spread over two domains: the 'social communication and interaction domain' and the 'restricted, repetitive behavior domain'. Autism is manifested by impairments in social skills, defective communication, stereotypic as well as repetitive behavior, restricted interests, confined activities and sensory difficulties. The global prevalence of ASD has considerably increased in recent years with one per 68 children afflicted with ASD [1]. Although, genetic factors appear to be strongly associated with the pathogenesis of ASD, yet several cases of autism can be attributed to non-hereditary factors. Exposure to teratogens after conception, adverse environment, prenatal viral/bacterial infections, gynecological interventions, etc. may all precipitate the risk of ASD in the offspring [2]. Due to high clinical and genetic heterogeneity, the pathogenesis of ASD continues to be a mystery making the treatment aspect of ASD a tough challenge. Clinical studies indicate that complementary therapies and rehabilitation approaches can partially alleviate some of the behavioral deficits, but they fail to reverse the entire core and associated symptoms of ASD. Therefore, a better understanding of the biomarkers, causative factors and pathology of ASD is warranted to develop effective treatment strategies for this enigmatic disorder.

Historical background

It is only in the last eight years (DSM-5) that Autism Spectrum Disorder has been precisely recognized, its specific characteristics described and diagnostic criteria updated. Paul Eugen Bleuler (a Swiss psychiatrist), Hans Asperger (an Austrian child specialist), Leo Kanner (an Austrian-American psychiatrist and social activist) and Grunya Sukhareva (a Russian lady-psychiatrist) deserve the credit for designating the term "autism" for the first time in the area of developmental disorders [1]. It is worthwhile to note that the clinical portrait of autism illustrated by Sukhareva is identical to the description of this disorder in the DSM-5 [3]. The earliest mention of autism in Indian history predates to 1944, by a Viennese child-specialist named A. Ronald, who worked in Darjeeling (West Bengal), using the term "abnormal children". India witnessed a sudden spurt in Autism related awareness since the late 1980s. The release of the film 'Rain Man', which bagged an Academy Award in 1988, turned out to be a crucial juncture for autism. This movie yielded a respectable international recognition to this childhood disorder with Indian film-goers being no exception. Tito Mukhopadhyay, an 11-year-old boy of Bangalore (India) suffering from autism, released his treatise, "Beyond the silence: My Life, the World and Autism", in 2000. The methods described in the book for training a child suffering from autism adopted by Tito's mother aroused a lot of interest globally. From the late 1980s, cognizance of autism in India has witnessed enormous growth in numerous domains including diagnosis, pharmacotherapy, herbal therapy and parental involvement, till today [1]. Over the past six decades, numerous autism surveys and studies have been conducted worldwide to discover the causes, consequences and possible therapeutic measures to treat this complex disorder.

Therapies for management of autism

Non-drug therapies

Therapeutic management of patients suffering from ASD is challenging. The patients suffering from autism spectrum disorder (ASD) experience difficulties in social communication and interaction in addition to involuntary stereotypic behaviors. While there is no good remedy in allopathy for ASD, complementary interventions are available that may be particularly beneficial when applied with adequate frequency and intensity by a professional therapist tailored as per the needs of the individual child [4]. Regardless of diagnosis, physicians recommend complementary therapies and healthy lifestyle practices in conjunction with allopathic measures for the integrative management of ASD symptoms, which are expressed in different ways in different individuals (Figure 1).

Complementary therapies

Complementary therapies include cognitive-behavioral therapy (CBT), applied behavior analysis (ABA), mindfulness-based interventions, educational therapy like speech exercises, language and communication training, vocational training and support, animal-assisted therapy (AAT), occupational therapy and psychotherapy (Figure 1). Complementary therapies aim at decreasing destructive and de-

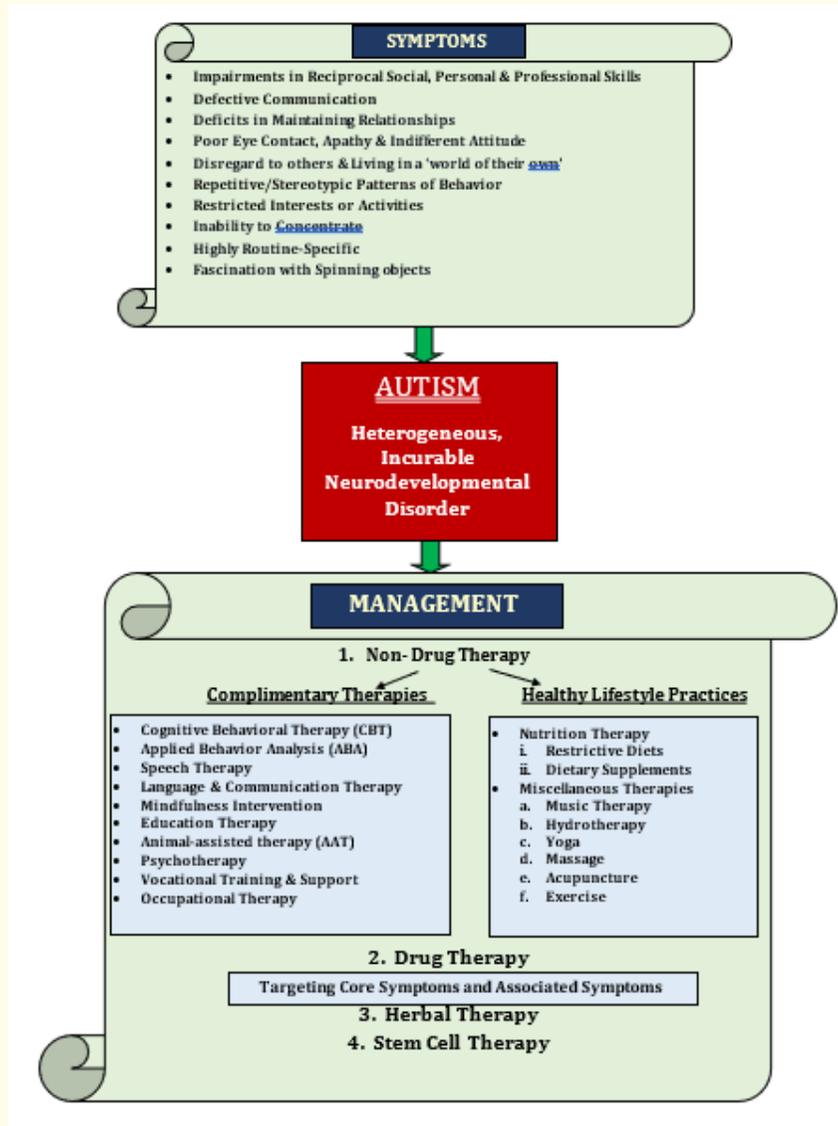


Figure 1: Integrative approaches for the management of autism.

pressive episodes, alleviating anxiety, improving self-expression, encouraging conversation, thereby facilitating sensory integration. Best results are obtained when complementary therapy intervention is tailor-made for each child and applied from the initial stage of ASD presentation soon after a confirmed diagnosis [5]. Appropriate interventions are advised for specific symptoms to be targeted. At present, Behavioral therapy remains the mainstay for the management of the basic/core symptoms of ASD. There are several types of behavioral therapies such as CBT, aversion therapy, ABA, system desensitization, etc. for treating mental health disorders. Applied behavior analysis (ABA) is administered to address difficulties in communication and social interaction as well as irregular response to sensory input. The goal of Behavioral therapy is positive reinforcement of desired behavior and breaking down tasks into simple steps with frequent rewards and corrections [6]. Behavioral interventions are moderate to highly effective in improving IQ scores, communication, social interaction,

language skills as well as irregular reaction to sensory input in children with ASD [7]. Cognitive-behavioral therapy (CBT) is a type of psychotherapeutic intervention that helps patients learn how to identify, change destructive/disturbing thought patterns that have a negative influence on behavior and emotions. CBT is based on the concept that one's thoughts, feelings, physical sensations and actions are interconnected. The negative thoughts and feelings trap one in a vicious cycle. CBT aims to help one and all in dealing with overwhelming problems in a positive way by breaking them down into smaller parts. CBT is a talking therapy, which deals with one's current problems rather than focusing on issues from the past. CBT is very helpful in improving the mental health of the child diagnosed with ASD. The goal of cognitive-behavioral therapy focuses on the betterment of concentration and behavioral patterns of the patient. CBT encourages the engagement of the patient with surrounding people and events [8]. Mindfulness appears to have broadly positive impacts on human functioning. Mindfulness is a "receptive attention to and awareness of present events and experience" [9]. The Mindfulness intervention helps in reducing distractions and improving attention, audio and visual focus, cognition, stability of mind and efficiency. Interventions based on mindfulness attempt to improve self-awareness, emotional quotient, positive outlook and create optimistic thoughts about life [10]. Cognitive-behavioral therapy (CBT) and mindfulness-based interventions are two primary intervention approaches of immense benefit to the children suffering from autism. An extension of ABA is parent-implemented training (PIT), in which parents are taught how to embed strategies to improve social communication of the child on daily basis [11]. Furthermore, the facilitation of parent-child interaction by language and communication therapy produces excellent outcomes in developing communication [5]. The children having symptoms of ASD show substantial benefits with educational interventions. Education therapy is used to treat individuals with learning difficulties/disabilities. ASD children differ in their capabilities to learn new things relative to their intellect and efficiency of sensory organs. Education therapy helps in overcoming learning problems and improving academic performance. Speech therapy is applied for the treatment of speech disorders and communication problems. It is administered by speech therapists or speech-language pathologists. Speech therapy helps in improving aphasia, dysarthria, expressive disorder, limited vocabulary, language disorder, fluency disorder, articulation disorder and receptive disorder. Animal-assisted therapy (AAT) is a new intervention through which many children can develop a relationship with animals. One form of AAT is equine-assisted activities and therapies (EAAT). Children get an opportunity to communicate in a complex nonverbal manner with horses (equine) in addition to developing a bond with them. Preliminary evidence with EAAT indicates that there are reductions in problematic behaviors such as irritability, hyperactivity, self-injury, etc. and a calming feeling is experienced by children after riding a horse. However, EAAT is an expensive therapy [12]. Psychotherapy when administered by a professional therapist has the potential to counter psychiatric symptoms such as obsessions, anxiety, minor or major depression, intellectual disability and aphasia [13]. The transition to adult life is one of the most important stages in an individual's life. Since ASD children exhibit defective social skills, compromised cognitive abilities and education, there is great difficulty in coping with the new phase and responsibilities of life when transitioning to adulthood. Vocational training offers great help in developing life skills in such individuals and Organizations have developed programs for the vocational training of adults with Autism Spectrum Disorder (ASD) [14]. Vocational training refers to instructional programs or courses that focus on the skills required for a particular job, trade, or career other than an academic subject. Occupational therapy including sensory integration (massage, pressure and brushing) and auditory integration therapies are also used by families to help develop skills needed for daily living [6]. Improvement in the cooperative attitude of the patient indicates the effectiveness of the therapy. The quality of the health care provider, the duration and the intensity of intervention also play an important role in the effectiveness of the intervention [15].

Healthy lifestyle practices

A healthy lifestyle can improve the mood and behavior of any person. Healthy lifestyle practices include proper nutrition, exercise, sleep, music, stress management and social relationships (Figure 1).

Nutrition therapy: Autism is such a disorder for which there is no cure in allopathy and "where there is no cure, one hundred treatments appear to work". Quality of food and lifestyle followed by expecting mothers appear to be linked with the occurrence of developmental disorders in the child-to-be born [16]. The daily diet consumed by the mother plays a critical role in having a healthy child. Regular intake of vitamin-rich diet and other nutritional supplements during pregnancy helps in reducing the risk of ASD, whereas high-fat diet consumption enhanced the risk of autism in the child. Several investigations have revealed that a carefully chosen diet succeeded in decreasing the magnitude of basic ASD symptoms [17,18].

Restrictive diets: Improvement in various ASD- associated co-morbid symptoms has been reported with certain dietary restrictions. Restrictive diets include a Ketogenic diet and a Gluten-free casein-free diet (GFCF).

The Ketogenic diet (KD): The KD is a diet that is rich in fat content and has extremely low levels of carbohydrates and proteins (e.g. kcal: 90% fat, 7% protein, 3% carbohydrates). There is evidence of positive clinical effects of KD, in addition to favorable pre-clinical findings [19-21]. KD improved the functioning of mitochondria and consequently reduced the ASD-associated abnormal behaviors [22].

Gluten-free casein-free diet (GFCF)/Exclusion diet: Diets free from gluten as well as casein are found to be beneficial in ASD patients [23]. It is worthwhile to note that peptides present in gluten and casein weaken immunity, trigger inflammation and damage the brain cells. The underlying mechanism for the beneficial effect of GFCF is related to reduced cytokine storm, strong immunity and intact brain function [24]. Furthermore, GFCF diets have been found to decrease sleep-related difficulties, gastrointestinal symptoms and improved conversation, attention and verbal expression [25]. Dietary restrictions run the risk of deficits in socialization, poor adherence and inability to meet needs for essential nutrients if improperly implemented. The GFCF diet should be monitored under the supervision of a registered dietitian to avoid poor adherence and food allergies. However, the GFCF diet adversely affected bone density because of deficiency of calcium and essential amino acids, leading to occasional bone fractures [18,26].

Dietary supplements: These are the items taken orally that contain one or more ingredients intended to supplement the diet and are not considered regular food. These can improve overall health and help manage health conditions.

Vitamins and minerals: Consumption of multi-vitamins and calcium supplements by women of child-bearing age reduced the risk of ASD in the newborn [27]. Intake of vitamins such as vitamin-B6, vitamin-B9, vitamin-B12, folate, magnesium and zinc is shown to be beneficial for the amelioration of core and associated symptoms of ASD in children [28-30]. Vitamin C has demonstrated improvement in quality of sleep, gastrointestinal symptoms and sensorimotor functions in children with ASD [31]. Vitamin D insufficiency and deficiency are commonly observed in children with ASD and lower levels are associated with severe symptoms. Supplementation with vitamin D is associated with improving symptoms in children with ASD [32,33].

Omega-3 fatty acids: Omega-3 fatty acids are essential polyunsaturated fatty acids, which are crucial for brain development and function. Food supplements consisting of omega-3 fatty acids are quite effective as compared to pharmacotherapy in improving social skills, reducing irritability and anger with minimal side effects [34].

Probiotics: Significant differences are reported between the gut microbiota of ASD children and healthy children. About 12% of ASD patients exhibit gastrointestinal abnormalities [35]. Probiotic supplementation has been considered a useful complementary intervention for the management of ASD in children. Several studies proved that certain live microbes confer health benefits when consumed in an adequate amount by the positive alteration of gut micro-flora [36,37]. Although probiotics decrease the gastrointestinal complaints in children suffering from ASD, they should not be prescribed in children with weaker immunity. Nevertheless, further research on the benefits of probiotics in ASD needs to be conducted [37].

Phytochemicals: Neuroinflammation is observed to be associated with impaired cognitive function observed in ASD children. Phyto-constituents like flavonoids and polyphenols are plant-derived compounds beneficial in reducing inflammation, producing an anti-oxidant effect and neuro-protection. In recent clinical studies, supplementation with flavonoids, like luteolin, quercetin and sulforaphane in children with ASD alleviated ASD-associated symptoms, improved gastrointestinal issues, eye contact, abnormal behavior, social responsiveness and verbal communication in ASD children [38,39]. Polyphenolic compounds like curcumin and resveratrol are also reported to produce favorable effects on autism symptoms. In preclinical studies, curcumin and resveratrol are found to reverse the behavioral symptoms of ASD in various animal models [40,41].

Camel milk: Recent studies suggested useful clinical effects of camel milk in the management of diabetes, hepatitis B, autism and other auto-immune diseases. Interestingly, camel milk ameliorated autism-related cognitive symptoms, improved emotional responses and rendered patients to be less destructive [42].

Diets to avoid/unhealthy diets: High-fat diet and food additives are found to aggravate the symptoms of ASD. So these should be avoided by children suffering from ASD. A high-fat diet (HFD) (different from KD) is a diet containing high fat, adequate protein and relatively low levels of carbohydrates (e.g. kcal: 60% fat, 20% protein, 20% carbohydrates). Cognitive impairment and social difficulties are found to be exacerbated with a high-fat diet in individuals suffering from autism [43]. A high-fat diet causes a substantial decrease in the dopaminergic transmission in the hypothalamus and nervous system that controls behavior, which probably results in behavioral defects related to autism [44]. Investigations revealed that food additives present in packed foods, particularly preservatives, coloring agents, flavoring agents and artificial sweeteners, have been associated closely with autism occurrence because of the presence of mercury in these foods. Therefore, intake of freshly prepared foods guarantees healthy newborns [45].

Intake of certain food items such as complex starches, processed foods and food additives by individuals suffering from ASD aggravate the symptoms of ASD, whereas GFCF diet, ketogenic diet, camel milk, probiotics and a diet containing curcumin, omega-3 polyunsaturated fatty acids, multi-vitamins, flavonoids, minerals, anti-oxidants, fresh vegetables and fermentable foods, not only help the expecting mother in the prevention of autism in the newborn but also help in ameliorating ASD symptoms developed in the child [46]. Acceptance of a general safety measure, regarding the selection of food items, is advocated to diminish ASD-associated social deficits and defective brain function, although sufficient evidence confirming the beneficial role of diet and nutritional supplements is lacking [30].

Miscellaneous therapies

Music therapy: Music therapy is an innovative, artistic, scientific and evidence-based method of restoring, maintaining and improving the emotional, physiological and psychological well-being of human beings of all ages and abilities through the power of music. Music serves as a battery charger for the human brain [47]. Music therapy is beneficial for improving interpersonal communication and depression. There are two methods of music therapy, namely improvisational music therapy (IMT) and singing/listening to songs [15,48]. Music therapy is associated with improvements in social interaction, verbal communication, initiating behavior and social-emotional reciprocity and increasing social adaptation skills and parent-child relationships in children with ASD [6,48].

Hydrotherapy: Hydrotherapy/water therapy comprises the use of water (hot, cold, steam, or ice) to relieve discomfort and promote physical well-being. This therapy can soothe sore muscles and joints, lower fevers, promote relaxation, ease labor pains, clear up skin problems and also stimulate the immune system of the body. Hydrotherapy is useful for high functioning children with ASD to provide a multisensory stimulus to promote activity, engagement, movement, relaxation, self-awareness and strength. Hydrotherapy has the most positive impact on the social behaviors of ASD children [49].

Yoga: Yoga is a movement therapy that could potentially ameliorate behavioral problems and anxiety. Yoga is found to correct maladaptive behavior and improve attention and concentration in children with ASD [50].

Massage: Massage therapy is often applied to counter anxiety, facilitate communication, socialization, reduce sensory impairment and improve sleep quality [51].

Acupuncture: Acupuncture is a form of Traditional Chinese Medicine in which needles are inserted in the skin and near tissues in specific points, known as acupuncture points. Acupuncture therapy has been reported to enhance motor skills, comprehension and cognitive functions in addition to being safe [52].

Exercise: Exercise is part of a healthy lifestyle. Physical exercise positively affects academic engagement and reduces stereotypy in children with ASD [53].

Drug therapy

Autism is manifested by impairments in social interactions, defective communication, stereotypic behavior, restricted interests, confined activities and sensory difficulties [1]. The core and associated symptoms of ASD exert a disastrous blow on the essential day-to-day functions of the patient [54]. The goal of the management of autism is to improve the quality of life of the patient and diminish family distress. 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 [54]. Despite the urgent need for a satisfactory remedy, there are no US-FDA-approved medicines, which ameliorate the core symptoms of ASD, particularly the deficits in reciprocal conversation and social skills [1]. Since a satisfactory therapeutic regimen is not available for the treatment of core symptoms of ASD, co-morbid conditions and ASD-associated symptoms are targeted [2,55]. To date, aripiprazole and risperidone are the only medicines approved by the US- FDA, for controlling ASD-associated behavioral disturbances, such as aggression, self-harm, severe tantrums, agitation, irritability and outbursts of ASD subjects [30]. However, these allopathic medicines show rewarding benefits only when applied in conjunction with complementary therapies. Different drugs that have been prescribed for the treatment of various ASD-associated symptoms include antipsychotics, serotonin reuptake inhibitors, lithium, clonidine, anticonvulsants, acetylcholinesterase (AChE) inhibitors, glutamate antagonists, GABA-ergic agonists, CNS-stimulants and antidepressants [30]. Medicines effective in the management of specific ASD-associated symptoms have been tabulated category-wise in table 1.

Drug Category	Medication	ASD symptoms targeted
Atypical Antipsychotics	Aripiprazole	Beneficial to treat aggressive episodes or self-injurious behaviors, irritability, outbursts; improvement in speech, hyperactivity and stereotypies
	Risperidone	
	Clozapine	
	Olanzapine	
	Ziprasidone	
	Paliperidone	
Long Acting Injectable Antipsychotics	Aripiprazole extended-release injectable	For Irritability and Aggression
	Risperidone long-acting injection	
	Paliperidone palmitate injection	
Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine	For the treatment of anxiety disorders and depression; improvement in social difficulties, maladaptive and repetitive behaviors
	Fluvoxamine	
	Sertraline	
	Loxapine	
	Escitalopram	
	Venlafaxine	
Anti-Convulsants	Divalproex	Improvement in irritability and repetitive behaviors
	Oxcarbazepine	Reduction in irritability and aggression
Tricyclic Antidepressants	Clomipramine	Improvement in social relatedness, obsessive compulsive and aggressive behaviors
Mood stabilizing agent	Lithium	Treatment of mood swings
Psycho-Stimulant	Methylphenidate	Improves hyperactivity, impulsivity and attention deficits

Norepinephrine Reuptake inhibitor	Atomoxetine	Improvement in hyperactivity
Alpha _{2A} Receptor Agonists	Clonidine	Improvements in hyperactivity, sleep onset and decreased night-time awakening
	Guanfacine	Reduction in hyperactivity, impulsivity and distractibility
Hormone	Melatonin	Reduction of sleep-related issues, improving sleep patterns; beneficial effects on anxiety, depression, pain and GI dysfunctions
	Oxytocin	Reduction in repetitive behaviors and improving social interaction
Acetylcholinesterase inhibitors	Donepezil	Improvement in behavior and language, reduction of irritability and hyperactivity
	Rivastigmine	
	Galantamine	
N-methyl-D-Aspartate (NMDA) glutamate receptor agonist	Ketamine	Decrease symptoms of depression and suicidality, reduction in aggressive behaviors
NMDA glutamate receptor antagonist	Amantadine	Improvement in hyperactivity, inappropriate speech, lethargy and irritability; beneficial in memory functioning
	Memantine	
Na-K-Ca co-transporter-1 (NKCC1) chloride-importer inhibitor	Bumetanide	Improvement in repetitive behavior and participatory social interaction
γAminobutyric Acid (GABA) Analogue	Acamprosate	Improvement in social behavior along with reductions in ADHD symptoms
Vasopressin 1a (V1a) Receptor Antagonist	Balovaptan	Improvement in social behaviors

Table 1: Drug therapy for the management of ASD- associated symptoms.

Management of irritability and aggression: Antipsychotics form the most popular medicines employed to control irritability and aggressive behaviors in patients suffering from ASD. Antipsychotics appear to be effective in long-term treatment for autism patients. Atypical antipsychotics, Aripiprazole and Risperidone are US-FDA-approved medicines for the treatment of irritability, severely disruptive behavior and aggressive episodes associated with ASD in children [30,55]. Newer antipsychotics viz. clozapine, olanzapine, ziprasidone and paliperidone are also useful in reducing irritability and aggression in children with autism despite their metabolic adverse effect of rapid weight gain [55]. Second-generation long-acting injectable antipsychotics such as sustained-release aripiprazole, long-acting risperidone and paliperidone, all effective at reducing irritation and hyperactivity can be administered by parenteral route in children with autism to overcome the difficulty of pill swallowing [55,56].

Management of mood, anxiety and depression: Anti-depressants and selective serotonin reuptake inhibitors (SSRIs) are often preferred to manage mood swings, anxiety, depression and abnormal behaviors associated with ASD. SSRIs like fluoxetine, fluvoxamine, sertraline, loxapine, escitalopram and venlafaxine demonstrate efficacy for improvements in social skills and maladaptive behaviors, which are well tolerated in adults with ASD [30,55]. A tricyclic antidepressant, clomipramine is beneficial in improving social interaction, obsessive-compulsive and aggressive behaviors in patients suffering from autism [30]. Mood stabilizing medication, lithium is a favorite option among physicians for treating mood swings manifested by mania or euphoria associated with ASD. Anticonvulsant agents like Divalproex and Oxcarbazepine are found to be effective in reducing both repetitive behaviors and irritability in children suffering from ASD [55].

Management of hyperactivity and inattention: The effectiveness of methylphenidate for children suffering from autism and ADHD symptoms has been confirmed with substantial benefits [30]. Amphetamine and lisdexamfetamine are often used to alleviate ADHD

symptoms of ASD [55]. Norepinephrine reuptake inhibitor Atomoxetine and Alpha 2_A receptor agonists like Clonidine and Guanfacine have been found to diminish hyperactivity, impulsivity, distractibility and maladaptive behavior in individuals suffering from ASD [55].

Management of sleep disorders: Sleep disorders are frequently observed in children suffering from ASD. The exogenous hormone melatonin is found to be efficacious in improving sleep quality, decreasing sleep latency and increasing sleep duration in children with ASD, with favorable action on anxiety, depression, pain and gastrointestinal upsets [30,55]. Clonidine is also found to be efficacious in improving sleep onset and decreasing night-time awakening in ASD patients [55].

Management of memory deficits: Acetylcholinesterase inhibitors like donepezil, rivastigmine and galantamine are found to be effective in improving memory, language and decreasing irritability and hyperactivity in children with ASD [30]. Piracetam, lamotrigine and dextromethorphan have also been reported to be useful in treating autism-associated symptoms to some extent.

Potential targets for discovering new medicines: Although, there is no specific cure for Autism Spectrum Disorder, several substances targeting glutamate/GABA imbalance, N-methyl-D-aspartate (NMDA) receptors, immune dysfunction, neuroinflammation, neuropeptides and endocannabinoid system are undergoing clinical trials with variable success.

Glutamatergic and γ -aminobutyric acid (GABA) modulating agents: The disturbance of the balance between glutamate, an excitatory neurotransmitter and GABA, an inhibitory neurotransmitter is thought to be involved in causing behavioral symptoms of ASD [54]. Compounds modulating the glutamatergic and GABA-ergic systems reduce overall cortical excitability and serve as potential targets for the basic symptoms of ASD. Ketamine, a non-competitive NMDA receptor agonist is found to be successful in reducing the tendency of committing suicides, aggressive behavioral episodes and social impairment [55]. The NMDA glutamate receptor antagonists, Amantadine and Memantine have been shown to improve memory and reduce maladaptive behavior in children with ASD [30,55]. Acamprosate, a GABA-analog and NMDA receptor modulator has been shown to produce substantial benefits in social interaction and ADHD-related symptoms in adolescents with ASD [55]. Latest clinical studies suggest that bumetanide, a loop diuretic acting via inhibition of Na-K-Ca co-transporter-1 chloride-importer and facilitation of GABA-ergic transmission to be a promising remedy for improving the core symptoms, such as repetitive behavior and reciprocal social interaction in ASD subjects aged 3 - 11 years old [57].

Immuno-modulatory agents: Modulation of the immune system is being targeted for discovering an effective medicine owing to the substantial association between immune dysfunction and ASD [55]. Cyclooxygenase-2 inhibitors and corticosteroids are being investigated for the management of ASD in preclinical and clinical studies [54]. A loading dose of intravenous (i.v.) immunoglobulin has been found to reduce biomarkers of brain inflammation and alleviate some clinical signs in children suffering from ASD [55,58].

Neuropeptides: Oxytocin and vasopressin are the two closely related endogenous neuropeptides, which play a crucial role in the maintenance of social activities and healthy relationships in addition to playing a critical role in the development of emotional bonds. Although the etiology of ASD is largely unknown, deficiency in the central Oxytocin system has been suggested to aggravate the symptoms. A randomized, crossover clinical trial showed that intranasal oxytocin significantly improved social interaction in ASD children below 8 years of age [59]. Balovaptan, a selective vasopressin 1a (V1a) receptor antagonist has been awarded a "Breakthrough Therapy" designation by the US-FDA as a therapeutic remedy to manage deficits in social interaction in children suffering from ASD. A systematic phase-III clinical trial using Balovaptan (NCT03504917) is currently underway in adults with ASD [55,60].

Endocannabinoid system: The endocannabinoid system appears to mediate social interaction and emotional responses impaired in ASD [61]. A well-designed clinical investigation in children suffering from ASD showed promising results after administration of cannabidiol and tetrahydrocannabinol (present in cannabis) [54].

Potential of medicinal herbs

Recent studies using medicinal herbs like *Asparagus racemosus* (Shatavari) [62,63], Ginkgo biloba [64] and Panax ginseng [65] showed promising anti-autistic potential in animals without any serious adverse effects.

Stem cell therapy

The stem cell therapy being highly invasive is not much likely to be adopted by the caretakers for the child suffering from ASD. The life expectancy of children suffering from autism can be enhanced by applying hematopoietic stem-cell therapies, which arrest neuronal apoptosis. Fetal stem-cell transplantation is being investigated as a useful surgical intervention for improving brain function and immune function in patients suffering from ASD [30].

Concluding Remarks

Autism spectrum disorder is a heterogeneous, multi-factorial, developmental disability with a dynamic set of metabolic, mitochondrial, immune, neuro-inflammatory and behavioral abnormalities that involves various parts of the body. Over the last century, research in Autism Spectrum Disorder (ASD) has undergone a constant revolutionary change. A sharp rise in the incidence of ASD cases has been noted worldwide of-late owing to the complex combination of increased awareness, broader diagnostic criteria, poor nutrition, various prenatal, perinatal and postnatal factors, genetic predisposition precipitated by adverse environmental conditions, the advanced age of parents and gynecological interventions. Autism spectrum disorder impacts adversely the day-to-day functioning of the child, thereby imparting considerable distress to the family. The established treatments for ASD core symptoms are still lacking. Despite the urgent need for a complete cure, there is no US-FDA-approved medication, which targets the basic symptoms of ASD, particularly the deficits of communication and social skills. Pharmacotherapy has shown limited benefits in addressing the core symptoms of ASD and innumerable non-pharmacological treatments have been suggested to help different aspects of this disorder. Since there is no satisfactory cure for ASD, a large segment of families dealing with ASD opt for non-drug therapies to help improve one or more symptoms. No single therapy fits exactly into all kinds of patients. Complementary therapies such as CBT, ABA, speech therapy, music therapy, educational therapy, psychotherapy, vocational therapy, occupational therapy and nutritional therapy have shown partial benefits when applied individually as per the specific needs of the child. Reassurance and re-evaluating each child are essential to yielding the best possible results. Most importantly compassionate care is crucial. A "precautionary principle" about food choices, during the antepartum and post-partum, is recommended to reduce the challenge of ASD- associated neuro-cognitive impairments. Although, there is no specific cure for ASD, several substances targeting immune dysfunction, neuroinflammation, glutamate/GABA imbalance, NMDA receptors and neuropeptides are undergoing clinical trials with variable success. Epidemiological surveys and study designs have to consider new methodologies, innovative experimental models and biomedical informatics to integrate clinical, environmental, genetic and epigenetic data to facilitate a better understanding of the molecular mechanisms involved in autism to establish better treatment approaches. To help the unfortunate child and improve the quality of life of concerned families, an integrative approach combining drug therapy and non-drug therapy aimed at ameliorating the primary and secondary symptoms of ASD offers a new ray of hope.

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Conflict of Interest

None.

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