AUTISM SPECTRUM DISORDER

[1]Kritigya Mishra, [2]Chandani Kumari
School of Pharmaceutical Sciences

Lovely Professional University

Punjab -144411

Abstact: Autism Spectrum Disorder (ASD) refers to a group of neurodevelopmental disorders including autism, Asperger's syndrome (AS) and pervasive developmental disorder not otherwise specified (PDD-NOS). The new diagnostic criteria of ASD focuses on two core domains: social communication impairment and restricted interests/repetitive behaviors. The prevalence of ASD has been steadily increasing over the past two decades, with current estimates reaching up to 1 in 36 children. Hereditary factors, parental history of psychiatric disorders, pre-term births, and fetal exposure to psychotropic drugs or insecticides have all been linked to higher risk of ASD. Several scales such as the Childhood Autism Rating Scale (CARS), The Autism Spectrum Disorder–Observation for Children (ASD-OC), The Developmental, Dimensional, and Diagnostic Interview (3di), are available to aid in better assessing the behaviors and symptoms associated with ASD. Nearly 75% of ASD patients suffer from comorbid psychiatric illnesses or conditions, which may include attention-deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, depression, Tourette syndrome, and others. Both pharmacological and non-pharmacological interventions are available for ASD. Pharmacological treatments include psychostimulants, atypical antipsychotics, antidepressants, and alpha-2 adrenergic receptor agonists. These medications provide partial symptomatic relief of core symptoms of ASD or manage the symptoms of comorbid conditions. Non-pharmacological interventions,which show promising evidence in improving social interaction and verbal communication of ASD patients, include music therapy, cognitive behavioral therapy and social behavioral therapy. Hormonal therapies withoxytocyin or vasopressin receptor antagonists have also shown some promise in improving core ASD symptoms.The use of vitamins, herbal remedies and nutritional supplements in conjunction with pharmacological and behavioral treatment appear to have some effect in symptomatic improvement in ASD, though additional studies are needed to confirm these benefits. Developing novel disease-modifying therapies may prove to be the ultimate intervention for sustained improvement of symptoms in ASD.

Keywords: Autism spectrum disorders, neurodevelopmental, Communication problem, Sleep disorders

Introduction: With an unexplained rise in incidence, autism spectrum disorders (ASD) are one of the greatest problems in modern medicine. According to figures from the Autism and Developmental Disorders Tracking Network of the CDC, approximately 1 in 68 children have been diagnosed with ASD [1]. “Autism” is derived from the Greek word “autos”, which means “self”. Eugen Bleuler, a Swiss psychiatrist, initially coined this term in 1908 to describe withdrawal from reality in patients with schizophrenia. In 1943, Leo Kanner redefined the term to describe symptoms of social isolation and linguistic disorders in children without schizophrenia or other known psychiatric disorders. Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors [2]. ASD is a heterogeneous collection of neurodevelopmental disorders with a common triad of symptoms: impaired social contact, disturbances of language and speech and stereotypical actions, which are characterized as ritualistic, repetitive, restrictive patterns of activities, behaviors and interests. Social anxiety disorder, oppositional challenge disorder, attention deficit/hyperactivity disorder, and intellectual disability are widely recognised psychological and cognitive comorbidities of ASD [3-5]. Frequently documented medical problems include defects of the immune system, gastrointestinal disorder, mitochondrial dysfunction, sleep disorders, and epilepsy [6-8]. Over the last two decades, the incidence of autism has risen dramatically from two to five per 10,000 children to 1:59 children (one in 37 boys and one in 151 girls), and the prevalence in males is four times higher than in females [9]. While the full spectrum of etiologies underlying ASD remains largely unknown, progress has been made in establishing certain neurobiological and genetic roots of this complex disorder and risk factors for it in the past decade. ASD is strongly inheritable, but environmental variables are also involved [10,11]. Several lines of evidence indicate that ASD etiology has prenatal origins [12]. ASDs have major direct and indirect effects in many fields, including health, education, social services, housing, jobs, welfare benefits and labour markets, with a high economic burden expanding to adulthood and mostly borne by families [13-14].

Epidemiology: The World Health Organization (WHO) reports that 0.76 percent of children worldwide have ASD; however, this only accounts for around 16 percent of the world's children (16). The Centre for Disease Control and Prevention (CDC) reports that 1.68 percent of 8-year-old children in the United States (US) have ASD (or 1 in 59 children). In the United States, parent-reported ASD diagnoses were marginally higher in 2016, averaging 2.5 percent (18). According to the Autism and Developmental Disabilities Monitoring Network (ADDM), the prevalence of ASD in the United States more than doubled between 2000 and 2012 (23). While it may be premature to make predictions about patterns, the prevalence of ASD in the United States appears to have stabilised, with no statistically significant increase from 2014 to 2016 (27). Changing diagnostic criteria could have an effect on prevalence, and the full impact of the DSM-5 diagnostic criteria is still unknown (25). ASD affects people of all races, ethnicities, and socioeconomic backgrounds, but its diagnosis varies widely. ASD is diagnosed more often in Caucasian children than in black or Hispanic children (23). Although the disparities seem to be narrowing, they may persist due to stigma, a lack of access to healthcare facilities, or the fact that a patient's primary language is not English. Males are more likely to have ASD (28,29) However, a recent meta-analysis (30), which did not use the DSM-5 criterion, found that the real male-to-female ratio is closer to 3:1 than the previously stated 4:1. This research also found that girls who meet ASD standards are more likely to go without a clinical diagnosis. Girls can be misdiagnosed, diagnosed later, or ignored due to the female autism phenotype. Females are not only less likely to appear with overt symptoms, but they are also more likely to conceal their social deficits through a mechanism known as "camouflaging," which makes a prompt diagnosis much more difficult (31). Gender inequalities and misconceptions about ASD as a male condition can also obstruct diagnoses. Several genetic diagnoses, such as fragile X, tuberous sclerosis, Down syndrome, and Rett syndrome, have a higher prevalence of co-occurring ASD than the general population; however, these identified genetic conditions account for a relatively small percentage of total ASD cases

(32-35). Males with sex chromosome aneuploidy have a complex social functioning profile that means they are more vulnerable to autism, according to studies (28,29,36,37). Several locations (chromosomes X, 2, 3, 7, 15, 16, 17, and 22 in particular) have been linked to an increased risk of ASD as a result of the increased use of chromosomal microarray (33). Prematurity and increased parental age are two other risk factors for ASD (38-40). This may be due to the theory that older gametes are more likely to bear mutations, which could lead to more obstetrical problems, such as prematurity (41).

Pathophysiology:

Though recent work in genetic epidemiology, imaging, molecular biology, and gross anatomy investigations have offered insights, the neurological pathways underlying the impairments found in ASD remain unclear. Early brain overgrowth has been linked to ASD in a number of studies, including a new meta-analysis (48). Functional integration has been shown to improve in imaging research, and hypoconnectivity across brain circuits is normal in people with ASD (45). Anatomic differences in brain substructures, especially in the cerebral cortex and cerebellum, are still being discovered, though the degree and direction of the differences recorded is variable (44, 46). Longitudinal imaging tests, as well as research into white matter integrity in particular brain structures, can help to explain neuroanatomic features that influence ASD behaviours (56). ASD has been linked to defects in metabolism, gut function, and immune function. Gastrointestinal signs have also been linked to more common difficult behaviours in children with ASD (43). However, there isn't a lot of agreement on the prevalence and causes of identified gut pathologies in kids with autism (42). In smaller subsets of ASD cases, defects in mitochondrial function, redox sensitive metabolism, and carbon metabolism have also been identified (47), but it is unclear how these multisystem comorbidities may help understanding of pathophysiology or possible etiologic subgroups.

Seizures and epilepsy: Epilepsy is more common in people with ASD than in people who are usually developing (49,50), particularly epilepsy that is resistant to normal therapies (51,52). Epilepsy is linked to higher rates of intellectual disability (49,53) more serious ASD symptoms (54), and higher mortality rates (55,56) particularly if it persists into adulthood (50). Genetic (57,58) and/or metabolic anomalies are often linked to epilepsy's underlying causes. Subclinical electrical discharges (SEDs) are particularly novel to children with ASD, with prevalence rates as high as 61 percent 51 and 100 percent 52 in trials using long-term electroencephalogram testing and magnetoencephalography, respectively. According to research, children with ASD who have SEDs have a distinct cognitive phenotype (67). In some cases, children with SEDs and ASD tend to be similar to children with epilepsy and ASD. When compared to children with ASD who do not have seizures, both are more likely to undergo deterioration, have an irregular developmental examination, and have brain lesions (63). And compared to children with ASD and SEDs, children with epilepsy and ASD are more likely to have developmental disability and greater levels of socialisation and hyperactivity (64,67).

Neurotransmitter disorders:

ASD has been linked to a variety of neurotransmitter defects. Monoamine neurotransmitters (such as dopamine, norepinephrine, and serotonin),17–19 amino acid neurotransmitters (such as glutamate and gamma-aminobutyric acid (GABA)), (70,71) and cholinergic (such as acetylcholine) neurotransmitters are among them (70). The causes of these neurotransmitter defects aren't always clear, although genetic variants that inhibit neurotransmission have been linked to ASD in animal models (72,73). Neurotransmission activity can also be disrupted by metabolic disruptions, some of which are discussed below. For example, central deficiencies in cofactors required for monoamine neurotransmitter development, such as folate16 (74), and tetrahydrobiopterin17–19, may cause monoamine neurotransmitter production to be disrupted. Glutamate synthesis may be disrupted by abnormalities in redox metabolism observed in the brains of children with ASD (75,76). Furthermore, some metabolic disorders linked to ASD may interfere with neurotransmitter activity directly (67,77). Succinic semialdehyde dehydrogenase deficiency, for example, has a direct effect on GABA (69) and mitochondrial abnormalities can impair GABA and acetylcholine neurotransmission (68). Oxytocin is a neurotransmitter that is increasingly being recognised as having a function in ASD, especially in terms of its role in social impairments (78). Autoantibodies, which are addressed further below, are sometimes present in children with ASD and may inhibit neurotransmission.

Sleep disorders: Prolonged sleep onset latency, frequent night time awakenings, reduced sleep duration, parasomnias, sleep disordered breathing, and daytime sleepiness are all common sleep abnormalities associated with ASD (79-81). Sleep disturbances have been linked to impaired social interaction, communication, behaviour, anxiety, and aggression (80-83) as well as a poor quality of life for the child and their family (84). Melatonin, the endogenous neurohormone best known for regulating sleep onset, has a disrupted concentration and circadian rhythm in ASD. 6-Sulfatoxymelatonin, the main metabolite of melatonin, is reduced in some children with ASD, implying decreased melatonin production (85-86) and concentrations are inversely related to the amount of deep (non-rapid eye movement) sleep (87). According to a recent study, N-acetylserotonin, the metabolite that comes before melatonin in the biosynthesis pathway, is increased in ASD and is inversely related to melatonin levels (88). Polymorphisms in acetylserotonin methyltransferase, the enzyme that converts N-acetylserotonin to melatonin, have been linked to disrupted circadian melatonin rhythms and lower melatonin concentrations in children with ASD and the parent(s) from whom the polymorphism was inherited, according to studies (89). As a result, some of the sleep problems associated with ASD appear to be caused by metabolic abnormalities in melatonin synthesis.

Metabolic disorders: Several metabolic disorders have been identified in people with ASD, and many of them have treatments (90). We'll go over some of the metabolic disorders that appear to affect at least a portion of children with ASD in the following sections.

- **Folate metabolism:** Many metabolic processes, such as redox metabolism and methylation, include folate. Polymorphisms that reduce the synthesis of 5-methyltetrahydrofolate and/or inhibit folate transfer through the blood–brain barrier and into neurons have been linked to ASD (91). Polymorphisms in the genes for methylenetetrahydrofolate reductase (92-100), dihydrofolate reductase (102), and the reduced folate carrier have been linked to ASD (100). The deficiency in folate transport through the blood–brain barrier caused by the malfunction of the folate receptor alpha (FR) is also important. Autoantibodies and mitochondrial dysfunction may also induce FR dysfunction. A high prevalence of FR autoantibodies (104) and mitochondrial dysfunction was related to ASD. If the FR is dysfunctional, it can lead to cerebral folate deficiency, which can lead to epilepsy, neurodevelopmental regression, autism, and neurological disorders like spasticity and coordination disorder. While mitochondrial dysfunction is not thought to be caused by FR autoantibodies, folate is important for mitochondrial function. Reduced folate supply in the brain may lead to mitochondrial dysfunction in the central nervous system (CNS).

- **Cobalamin metabolism:** While blood cobalamin concentrations have been confirmed to be both decreased and increased in the ASD population, abnormalities in cobalamin-dependent metabolism have been linked to ASD (100). However, a recent study found lower cobalamin concentrations in postmortem brain samples from people with ASD when compared to controls, implying that ASD is linked to a cobalamin deficiency in the brain (110). Methionine, homocysteine, and cysteine, which are partly dependent on cobalamin in the methylation and glutathione pathways, have been confirmed to be abnormal in some people. Furthermore, studies have found polymorphism in cobalamin-related genes such as methionine synthase, a cobalamin-dependent enzyme, and transcobalamin, the cobalamin transporter (100). Methionine synthase activity was found to be substantially lower in brain samples from people with autism relative to age-matched controls in a recent study (110).
- **Tetrahydrobiopterin metabolism:** Tetrahydrobiopterin (BH4) is a naturally occurring molecule that is needed for several metabolic pathways, including the development of monoamine neurotransmitters, phenylalanine breakdown, and nitric oxide production. When oxidative stress is present, such as in ASD (106), BH4 is easily oxidised by reactive species, resulting in its destruction (105). The concentration of BH4 in the cerebrospinal fluid has been found to be low in some people with ASD (105,106). Thus, reduced CNS BH4 concentrations may be to blame for ASD-related CNS monoamine neurotransmitter and nitric oxide disturbances.
- **Carnitine metabolism:** While carnitine deficiency is common in children with ASD, the children with ASD and carnitine deficiency have not been well studied (108). Seven children with ASD were recently found to have a defect in the TMLHE gene, which codes for the first enzyme in the carnitine biosynthesis pathway (109). This genetic defect was much more prevalent in probands from male–male multiplex ASD families, but not in ASD children in general, implying that it was not a causative mutation but rather a factor that interacts with other genetic and/or environmental influences. Fatty acid metabolism disorders, including carnitine metabolism, have also been identified in people with ASD (107,111). Since carnitine metabolism is essential for the transportation of short-chain fatty acids generated by the microbiome, a carnitine deficiency could be caused by imbalances in the host-microbiome interactions (107,112). Considering that mitochondrial disease (MD) and dysfunction can impair carnitine metabolism, carnitine deficiency may be a side effect of MD.

Immune disorders: Many lines of evidence refer to the immune system as being involved in ASD. Prenatal exposure to lipopolysaccharide, for example, causes a maternal immune response in traditional animal models of ASD (113,114). In one remarkable study, symptoms in a mouse model of Rett syndrome were substantially reduced after the mice received bone marrow transplantation from a wild mouse.

GI disorders: Up to 91 percent of children with ASD experience a series of gastrointestinal symptoms that can be debilitating individuals (115,116). A recent study showed that children with ASD were more likely than normally developing children and children with developmental delays without ASD to have constipation, diarrhoea, or food allergy and/or intolerance (117). Other research has linked ASD to specific GI dysfunctions, such as irregular carbohydrate transport through enterocytes (118) and nonspecific inflammation (115,116) individuals. The trillions of microbes that reside in the human digestive tract, known as the enteric microbiome, are thought to influence immune and metabolic functions, modulate gene expression, and play a role in brain and behavioural growth.

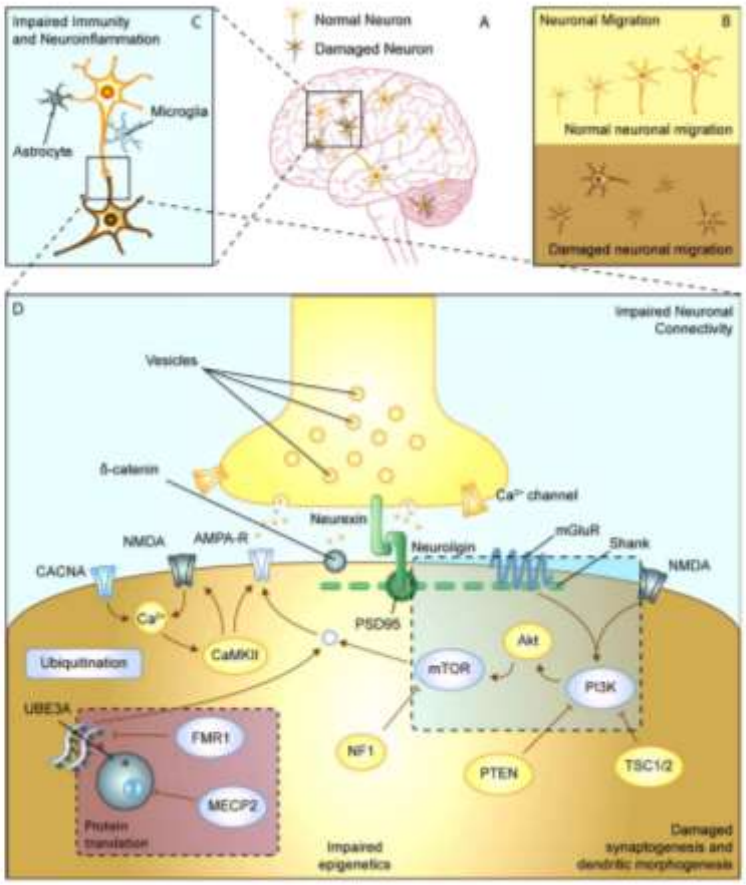

Fig. Summary of proposed converging mechanisms of autism spectrum disorders.

Risk Factors: ASD is a neurobiological disease induced by genetic and environmental effects on the developing brain. Current research is deepening our understanding of possible etiologic pathways in ASD, but there is currently no single unifying cause.

Cerebellar structure and connectivity differences, limbic system defects, frontal and temporal lobe cortical changes, and other subtle malformations have all been discovered in neuropathologic research (119,121,122). A small exploratory analysis of neocortical architecture in young children showed that the majority of participants had focal disruption of cortical laminar architecture, indicating issues with cortical layer formation and neuronal differentiation (123). Brain enlargement, both in terms of cortical size and also in terms of increased extra-axial fluid, has been identified in children with ASD and is a subject of ongoing research, both to better understand the aetiology of the condition and as a possible biomarker (124,125).

ASD sensitivity is affected by genetic factors, with siblings of ASD patients having a greater probability of diagnosis than the general population, and a much higher, but not total, concordance of autism diagnosis in monozygotic twins (126-128). We now have a better understanding of ASD susceptibility genes due to genome wide association studies and whole exome sequencing methods, and learning more about the role of these genes will shed light on possible biologic mechanisms (129). Candidate genes in ASD, for example, include those involved in brain growth or neurotransmitter regulation, as well as genes that influence neuronal excitability (130,131),

Although genetics obviously play a role in the aetiology of ASD, the phenotypic expression of genetic vulnerability within the condition is extremely variable (132). In some patients, prenatal, perinatal, and postnatal environmental factors can influence genetic risk. Prenatal exposure to thalidomide and valproic acid has been linked to an increased risk, although studies indicate that prenatal folic acid supplements may reduce risk in patients taking antiepileptic drugs (133-135). There hasn't been any study conducted to see whether a small positive trial of folinic acid in autism can be used to suggest supplementation to the general public (136). Both advanced maternal and paternal age have been linked to an increased risk of having an ASD infant (137). A history of autoimmune disease in the mother, such as diabetes, thyroid disease, or psoriasis, has been suggested, but research findings are mixed (138,139). Another field of study is maternal infection or immune activation during pregnancy, which may be a risk factor, according to recent studies (140-143). Shorter and longer inter-pregnancy periods have been linked to an increased risk of ASD (144). Premature birth has been related to an increased risk of ASD and other neurodevelopmental disorders in children (120). Obstetric factors such as uterine bleeding, caesarian delivery, low birth-weight, preterm delivery, and low Apgar scores were stated to be the few factors more consistently associated with autism in a previous epidemiologic study (145).

Finally, research continues to uncover factors that are linked to the risk of ASD, but no causal conclusions have been reached. With investigators continuing to elucidate new variants conveying genetic risk or new environmental correlates that need further research, there is a lot of space for new discoveries (146).

Symptoms:

By 12 months - Does not respond to name

By 14 months - Does not point at objects to show interest

By 18 months - Does not pretend play

General - Avoids eye contact and may want to be alone

- Has trouble understanding other people's feelings or talking about their own feelings
- Has delayed speech and language skills
- Repeats words or phrases over and over (echolalia)
- Gives unrelated answers to questions
- Gets upset by minor changes
- Has obsessive interests
- Makes repetitive movements like flapping hands, rocking, or spinning in circles
- Has unusual reactions to the way things sound, smell, taste, look, or feel.

Diagnosis of ASD: Because of the difficulty, severity, and correlation of ASD symptoms with those of other psychiatric conditions, it is vital to accurately diagnose ASD using suitable tools and scales in order to facilitate clinical treatment of ASD patients. Parent/caregiver interviews, patient interviews, direct evaluation of patients, and comprehensive clinical tests that include a thorough analysis of family history for ASD or other neurodevelopmental disorders are all used as assessment tools. Vllasaliu et al., 2016 (147) include an authoritative overview of these scales. The following are some of the most frequently used scales to diagnose ASD.

1. **The developmental, dimensional, and diagnostic interview:** The 3di (Developmental, Dimensional, and Diagnostic Interview) is a computer-assisted interview with parents and caregivers. It contains 740 items, including 183 questions about demographics, 266 questions about ASD symptoms, and 291 questions about possible comorbidity with other disorders (148). The answers are graded on a scale of "0" (no evidence of impaired behaviours) to "2" (evidence of impaired behaviours) (definite evidence of such behavior). The 3di can be used to diagnose people with ASD at any age, from infancy to adulthood, and the assessment usually takes 1.5 to 2 hours (148).
2. **Childhood Autism Rating Scale (CARS):** The Childhood Autism Rating Scale (CARS) is a widely used scale for assisting in the diagnosis of ASD in children (149). It can tell the difference between children who have autism and others who have other developmental disabilities, such as mental retardation. CARS has also been shown to be effective in diagnosing ASD in adolescents and adults in another research. CARS consists of 15 products that cover multiple ASD symptoms and allows for a consistent comparison of an affected child's activities and abilities to a healthy child's predicted developmental growth. Each object is given a score ranging from "1" (normal behaviour) to "4" (abnormal behaviour) (severely abnormal behavior). Mild to moderate ASD is indicated by a score of 30 to 37, while extreme ASD is indicated by a score of 38 to 60 (149).

3. **The Autism Spectrum Disorder–Observation for Children:** The Autism Spectrum Disorder-Observation for Children (ASD-OC) is a 45-item observation scale used to observe and rate core autistic symptoms such as social dysfunction, communication delays, and repetitive behaviours in children with autism. Individuals with ASD have their activities compared to children of the same age group and are given a score of "0" (no impairment), "1" (mild impairment), or "2" (severe impairment). A recent clinical review confirmed the ASD-clinical OC's validity as a reliable scale for assessing ASD symptoms in children aged 3 to 15 years (150).
4. **The Autism Diagnostic Interview-Revised:** The Autism Diagnostic Interview-Revised (ADI-R) is a research-based interview for parents/caregivers of children and adults who are suspected of having autism or ASD. It includes 93 elements that measure individual behaviours at various ages, such as mutual social contact, language and communication, stereotyped repetitive behaviours or interests, and age-of-onset requirements. It is usually scored on a scale of "0" (no evidence) to "3" (extreme severity of affected behaviour), takes 2–3 hours to complete, and is only suitable for children aged 2 and up (151).
5. **The Asperger Syndrome Diagnostic Interview:** The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI) is a 15–20 minutes investigator-based interview designed to help doctors decide whether a patient fits the diagnostic criteria for autism or AS. It has 20 items divided into six categories: (A) verbal and speech disorders (5 items), (B) nonverbal communication problems (5 items), (C) social contact disorder (4 items), (D) limited interests (3 items), routines (2 items), and motor clumsiness (2 items) (1 item). An individual must have a definite score in three items in group A, two items in group C, and at least one item in groups B, D, E, and F to be diagnosed with AS or high-functioning autism (152).
6. **The Diagnostic Interview for Social and Communication Disorders:** The Diagnostic Interview for Social and Communication Disorders (DISCO) is a semi-structured interview for parents and caregivers that is used to diagnose children and adults with ASD. It offers a developmental assessment of patients' social activity, abilities, and communication from infancy to adulthood (153). The DISCO, which takes 2 to 3 hours to complete, employs a dimensional approach to evaluation rather than cut off points, and is designed to monitor patterns of impairments in social behaviours and speech in people suspected of having ASD symptoms over time.
7. **Autism Spectrum Disorder–Diagnosis Scale for Intellectually Disabled Adults:** Adults with intellectual disability (ID) and ASD are separated using the Autism Spectrum Disorder–Diagnosis Scale for Intellectually Impaired Adults (ASD-DA) (154). The ASD-DA is a 31-item questionnaire that encompasses the three core deficits (social disability, communication deficits, and restricted interests). It can be completed in 10 minutes and is usually graded as "0" (no impairment) or "1" (significant impairment) (impairment). A cut-off score of 19 denotes comorbid ASD, while a score of b19 denotes ID without ASD (154).

Management and Treatment:

1. **Pharmacological therapies for ASD:** Pharmacological and non-pharmacological interventions are currently available for ASD care. Psychostimulants, atypical antipsychotic medications, antidepressants, alpha-2 adrenergic receptor agonists, cholinesterase inhibitors, NMDA receptor antagonists, and antiepileptic mood stabilisers are all examples of pharmacological treatments (155). This section addresses the most widely prescribed medications for the treatment of paediatric and adult ASD patients, as defined in double-blind, randomised, placebo-controlled trials (RCTs), retrospective open-label clinical trials, or pilot studies.

- Psychostimulants: Since ASD and ADHD have such a high level of co-morbidity, conventional ADHD psychostimulant medications like methylphenidate and amphetamines tend to be successful in treating ADHD symptoms in ASD patients (156). Earlier double-blind, crossover RCTs indicated that methylphenidate could be helpful in the treatment of hyperactivity in children with ASD, but the latter study identified a rise in adverse events like social isolation and irritability (157). The Research Units on Pediatric Psychopharmacology (RUPP) Autism Network indicated that methylphenidate was successful in reducing hyperactivity and impulsivity in 50% of 72 children with ASD (ages 5–14 years) who also had hyperactivity in a larger crossover RCT. Another study in preschool-aged children found that twice-daily methylphenidate dosing (range 2.5–10 mg or 0.14–0.58 mg/kg for both the morning and noon doses) reduced hyperactivity and impulsivity by 50%; higher doses were associated with a higher incidence of side effects such as irritability and stereotypic habits, gastrointestinal and sleep issues. Psychostimulants were found to be most successful in enhancing comorbid hyperactivity and impulsivity in ASD patients, but had little impact on other symptoms such as irritability, social isolation, repetitive activities, or speech impairment.
- Atypical antipsychotic drugs: Atypical antipsychotic medications have a broad range of affinities for dopamine, serotonin, and other neurotransmitter receptor subtypes, and are commonly used to treat schizophrenia and other psychotic disorders (158). Risperidone, aripiprazole, quetiapine, ziprasidone, and to a lesser degree olanzapine are the most widely prescribed atypical antipsychotic medications for ASD patients (159).
- Antidepressant drugs: Antidepressant drugs, especially SSRIs, are commonly prescribed to ASD patients, and their use has been increasingly growing, despite inconclusive, and in many cases poor, evidence supporting their benefits in improving core ASD symptoms or comorbid depression and anxiety (160) Among the most commonly prescribed SSRIs in ASD are fluoxetine, sertraline, citalopram, escitalopram, and fluvoxamine (161).
- Alpha-2 adrenergic receptor agonists: Aggressive actions, sleep disturbances, and anxiety are all common symptoms in ASD patients, and alpha-2 adrenergic receptor agonists have been related to their care (162). These drugs block norepinephrine neurotransmission in the brainstem, resulting in a reduction in sympathetic outflow and peripheral resistance, reducing hyperarousal, anxiety, and/or motor spasm. In a previous double-blind, crossover RCT, the alpha-2 adrenergic receptor agonist clonidine was found to minimise hyperarousal activities and increase social interactions in young ASD patients after four weeks of therapy. Another double-blind RCT found that clonidine therapy reduced irritability and hyperactivity in children with ASD. Clonidine was found to be successful in reducing sleep initiation latency and night waking, as well as, to a lesser extent, improving hyperactivity and aggressiveness in ASD adolescents, in a third open labelled retrospective clinical trial with a relatively benign tolerability profile (163).

  Another alpha-2 receptor agonist, guanfacine extended release (guanfacine-ER), has also been studied in ASD. In a randomised controlled trial, symptoms of hyperactivity, impulsivity, and distractibility in ASD children treated for 8 weeks with guanfacine-ER were significantly improved relative to placebo-treated patients (164). Drowsiness, exhaustion, and a lack of appetite were among the side effects. Another double-blind RCT found that guanfacine improved hyperactivity in ASD children when compared to placebo controls. However, drowsiness, exhaustion, and reduced appetite were recorded in both studies, suggesting that caution should be exercised when prescribing this agent to ASD patients (165).

2. **Non-pharmacological therapies for ASD**:

- **Complementary and integrative health:** Despite the increasing incidence of ASD in the United States over the last several decades, currently available pharmacologic treatments have varying degrees of effectiveness and are only capable of minimising the symptoms of the disorder's debilitating repetitive activities rather than altering the underlying disease mechanism (166). Concerns about the side effects of atypical antipsychotics, which are widely used as first-line pharmacotherapy in ASD, combined with a desire to identify therapies that can effectively change the underlying neurodevelopmental disorders present in children with ASD, has sparked a surge in interest in complementary and integrative health (CIH), previously known as complementary and alternative medicine, to augment traditional treatment practices (167).
  The National Center for Complementary and Integrative Health (NCCIH), a division of the National Institutes of Health (NIH), divides complementary and integrative health approaches into two categories: mind/body practises and natural products, stressing that complementary practises are frequently used in combination with conventional medical practises rather than as a substitute for them, while integrative health represents the convergence of complementary and integrative health practises (168).
- **Music therapy:** Music therapy may be particularly successful in ASD because of its remarkable ability to alter both the structure and functional connectivity of the cortex in early developmental stages, allowing for greater multisensory integration through cortical and subcortical domains, which is commonly believed to be the central underlying neurophysiologic aberration in ASD (169). Patients with ASD also have a retained, if not heightened, sense of musicality that lasts into adulthood, with the ability to perceive and respond to the emotions expressed in song or music even though they are unable to do so verbally (170). Shard and colleagues discovered a neurophysiologic correlate for this in 2014 when they discovered that 22 children with ASD, with varying degrees of functioning, triggered bilateral temporal brain networks during sung-word perception, similarly to an age and gender-matched control group, and that functional front-temporal integration, which was impaired during spoken-word perception, was maintained during sung-word perception (171).
- **Cognitive-behavioral therapy:** CBT is a psychotherapeutic intervention that has been shown to be effective in the treatment of a variety of mental conditions, including anxiety, depression, and OCD (172). CBT is particularly appropriate for ASD patients because of its highly organized and predictable nature, which makes it suitable for both core symptoms and comorbid anxiety and depression. In general, these services provide psychoeducation as a central component, as well as social coaching to assist in the development of social skills, self-care training, and highly organised worksheets and visual aids (173). ASD patients have modified CBT procedures and protocols to treat symptoms and complications resulting from their condition that would interfere with the implementation of standard CBT, such as their difficulties in identifying and interpreting both their own and others' thoughts and feelings (174).
- **Social behavioral therapy:** SBT aims to improve functional independence and quality of life in people with ASD by focusing on the improvement of emotional control, social skills, and communication. Specific focused approaches focusing on each symptom area, as well as more nuanced and systematic approaches, are examples of SBT interventions (175). Applied Behavioral analysis (ABA) is an experimental approach that evaluates the impact of environmental events on behaviour and employs structured specific teaching methods focusing on language, cognitive, sensorimotor skills, social interactions, everyday living skills, and specific problem behaviors (176).
- **Herbal medicine:** Several herbal remedies, including Gingko biloba, Zingiber officinale (ginger), Astralagus Membranecaeus, Centella asiatica (gotu cola), and Acorus Calamus (Calamus), may have therapeutic benefits in ASD patients due to their somatic effects, which include increasing cerebral circulation, improving cognitive functions, exerting a calming or sedative effect, and enhancing immune response (177). Herbal drugs, when used in conjunction with traditional therapy, showed positive results in improving abnormal habits and inattention in ASD patients, according to a new systematic study. However, due to issues with the methodological consistency of the included studies, such results should be viewed with caution (178).

Case Study: Leo Kanner published a paper in 1943 entitled " Autistic Affective Contact Disorders " describing eleven case studies of children (eight males and three females) from 2 years of age and 4 months to 11 years of age who were present at his clinics [15]. Kanner described these children's observations as having an intense inability to relate to others that seemed to be present during childhood. Based on the time of onset, Kanner drew a distinction between this syndrome and that of "childhood schizophrenia" as childhood schizophrenia was defined as withdrawal after normal development. In addition to this desire for isolation, Kanner also noticed unusual development of language, with a capacity for nouns and nursery rhymes to understand, a failure to improve the communicative features of speech, a tendency to exhibit echolalia, and a tendency to literally perceive items, along with sensory sensitivities and repetitive behaviors.

Hans Asperger published a paper in 1944 which described what he called " autistic psychopathy ". This paper identified children who mostly had nonverbal communication and associated social skills difficulties. Ultimately, this paper can be considered as significant as the work of Kanner in developing the concept of autism, because the core symptoms were the same as those found by Kanner but in higher-functioning people [16-17].

As an endorsed medical condition, infantile autism first appeared in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [18] and identified a subgroup of pervasive developmental disorder (PDD) [19]. For Infantile Autism, the requirements described required an onset before the age of 30 months, an inability to respond to others, gross deficiencies in language growth, and bizarre reactions to environmental stimuli, with no symptoms of schizophrenia. In the DSM-III-R, the criteria were broadened to reflect the omnipresent existence of the condition and that it was not confined to children, as the criteria for Infantile Autism omitted a subgroup of higher-functioning people who exhibited the mentioned deficiencies but did not exhibit the symptoms early enough in life to obtain the diagnosis.

The DSM-IV for the diagnosis of autistic disorder was published in 1994 with parameters similar to the DSM-III-R, however the childhood onset specificator was omitted as required before 36 months of age. Using some of the criteria outlined by Wing, the DSM-IV implemented a formal set of criteria for Asperger's Syndrome [20]. A condition with impairments in social interaction, communication, and creativity was defined by the criteria for Asperger's Syndrome, similar to that mentioned by the criteria for autistic disorder, but without impairments in language or cognition [21].

The transition to DSM-5 was characterized by an extension of the concept and a decrease in the specificity of autism-related symptoms [22], suggesting major improvements in the diagnostic criteria.

The number of different conditions with the term Autism Spectrum Disorder, the lack of understanding regarding the relationship between functional levels of autism and diminished cognitive function, and the diagnostic significance and need for care for certain people who tend to demonstrate higher levels of occupational and intellectual functions continue to be widely debated.

Conclusion: ASD is a neurodevelopmental condition marked by social communication problems as well as limited interests and repetitive activities. The move to the latest diagnostic manual (DSM-5) resulted in recent revisions to the diagnostic criteria, which are likely to have an effect on prevalence, which currently stands at 1 in 59 children in the United States. Over the last 20 years, the prevalence of ASD has gradually increased, with recent estimates reaching as high as 1 in 36 children, with boys having a 4-fold higher risk of developing ASD than girls. While the availability of various scales has refined the evaluation method and helped in diagnostic clarity, ASD diagnosis remains clinically subjective to a large degree. Scales can be used to diagnose people with ASD at various developmental stages, from early childhood to adulthood, and can also be used to distinguish between ASD and other developmental disorders. ASD treatments include both pharmacological and non-pharmacological approaches. Psychostimulants including methylphenidate and amphetamines are used to treat comorbid hyperactivity and impulsivity in ASD patients, but they have no effect on the central symptoms of the disorder. Risperidone, aripiprazole, quetiapine, ziprasidone, and olanzapine are atypical antipsychotic medications that are effective in reducing irritability and anxiety in ASD patients. Because of their negative side effects, such as metabolic deficits and sedation, caution is advised when prescribing these drugs, particularly for young ASD patients. Antidepressant medications (fluoxetine, sertraline, citalopram, escitalopram, and fluvoxamine) are also provided to ASD patients to help with repetitive activities, anxiety, and violence, but the overall therapeutic effects of these drugs are unknown. Other pharmacological agents, such as the alpha-2 adrenergic receptor agonists clonidine and guanfacine extended release, have been shown to help ASD patients with violent activities, anxiety disorders, and sleep disturbances. Non pharmacological therapy includes music therapy, cognitive and social behavioral therapy, herbal medicines.

While reliable tests to validate the diagnosis have yet to be established, the rapid increase in the occurrence of ASD among children may be due to improved diagnosis of the condition due to improvements in the accuracy of commonly used scales. The availability of these tests, or the identification and validation of selective biomarkers for ASD, would improve the accuracy of ASD diagnosis, potentially increasing the disorder's prevalence beyond the estimated 1 in 36 children or providing greater consistency in assessing clinical presentation and prognosis. The available pharmacological and non-pharmacological therapies tend to relieve some of the disease's core symptoms and allow better control of the comorbid conditions that are common in ASD patients. Although significant progress has been made in understanding the disease's developmental pathophysiology, real disease-modifying agents have yet to be discovered. Novel and much-needed disease-modifying therapies that can dig deeper into the disorder's core deficits and normalise or prevent its expression can prove to be the ultimate intervention for improved ASD care.

References:

1. Yenkoyan, K., Grigoryan, A., Fereshetyan, K. and Yepremyan, D., 2017. Advances in understanding the pathophysiology of autism spectrum disorders. *Behavioural brain research*, *331*, pp.92-101.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing, 2013.
3. 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: 921–929.
4. Mannion A, Leader G. An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with autism spectrum disorder: A two-year follow-up. Res Autism Spectr Disord 2016, 22: 20–33.
5. Matson JL, Shoemaker M. Intellectual disability and its relationship to autism spectrum disorders. Res Dev Disabil 2009, 30: 1107–1114.
6. Bauman ML. Medical comorbidities in autism: Challenges to diagnosis and treatment. Neurotherapeutics 2013, 7: 320–327.
7. Mannion A, Leader G. Comorbidity in autism spectrum disorder: A literature review. Res Autism Spectr Disord 2013b, 7: 1595–1616.
8. Zerbo O, Leong A, Barcellos L, Bernal P, Fireman B, Croen LA. Immune mediated conditions in autism spectrum disorders. Brain Behav Immun 2015, 46: 232–236.
9. Baio, J.; Wiggins, L.; Christensen, D.L.; Maenner, M.J.; Daniels, J.; Warren, Z.; Kurzius-Spencer, M.; Zahorodny, W.; Robinson Rosenberg, C.; White, T.; et al. Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill. Summ. 2018, 67, 1.
10. Gupta S, Ellis SE, Ashar FN, Moes A, Bader JS, et al. 2014. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nat. Commun. 5:5748
11. Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK, Windham GC. 2014. Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions. Am. J. Psychiatry 171:1206–13
12. Bauman ML, Kemper TL. 2005. Neuroanatomic observations of the brain in autism: a review and future directions. Int. J. Dev. Neurosci. 23:183–87
13. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatrics 2014, 168: 721–728.
14. Ganz ML. The lifetime distribution of the incremental societal costs of autism. Arch Pediatr Adolesc Med 2007, 161: 343–349.
15. Kanner L. Autistic disturbances of affective contact. Nervous Child 1943, 2: 217–250.
16. Asperger H. Die Autistischen Psychopathen im Kindesalter. Arch Psychiatr Nervenkr 1944, 117: 76–136. Trans. U. FRITH in U. FRITH (ed.). Autism and Asperger Syndrome. Cambridge: Cambridge University Press, 1991: 37–92.
17. Silberman S. NeuroTribes: The Legacy of Autism and How to Think Smarter About People Who Think Differently. Allen & Unwin, 2015.

18. APA. Diagnostic and Statistical Manual of Mental Disorders. Third Edition. Washington, DC: American Psychiatric Association, 1980.
19. Volkmar FR, Cohen DJ, Paul R. An evaluation of DSM-III criteria for infantile autism. J Am Acad Child Psychiatry 1986, 25: 190–197.
20. Wing L. Asperger's syndrome: a clinical account. Psychol Med 1981, 11: 115–129.
21. APA. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, DC: American Psychiatric Association, 1994
22. APA. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC: American Psychiatric Association, 2013.
23. 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 Surveill Summ 2018;67:1-23.
24. 16. Baxter AJ, Brugha TS, Erskine HE, et al. The epidemiology and global burden of autism spectrum disorders. Psychol Med 2015;45:601-13.
25. Palinkas LA, Mendon SJ, Hamilton AB. Annual review of public health innovations in mixed methods evaluations. Annu Rev Public Heal 2019;40:423-42.
26. Kogan MD, Vladutiu CJ, Schieve LA, et al. The prevalence of parent-reported autism spectrum disorder among US children. Pediatrics 2018;142:e20174161.
27. Xu G, Strathearn L, Liu B, et al. Prevalence of autism spectrum disorder among US children and adolescents, 2014-2016. JAMA 2018;319:81.
28. Demily C, Poisson A, Peyroux E, et al. Autism spectrum disorder associated with 49,XYYYY: case report and review of the literature. BMC Med Genet 2017;18:9.
29. 23. Tartaglia NR, Wilson R, Miller JS, et al. Autism spectrum disorder in males with sex chromosome aneuploidy: XXY/ klinefelter syndrome, XYY, and XXYY. J Dev Behav Pediatr 2017;38:197-207.
30. Loomes R, Hull L, Mandy WPL. What is the male-tofemale ratio in autism spectrum disorder? A systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2017;56:466-74.
31. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2014;53:237-57.
32. Sztainberg Y, Zoghbi HY. Lessons learned from studying syndromic autism spectrum disorders. Nat Neurosci 2016;19:1408-17.
33. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics 2007;120:1183-215.
34. Reddy KS. Cytogenetic abnormalities and fragile-X syndrome in autism spectrum disorder. BMC Med Genet 2005;6:3.
35. Yoo H. Genetics of autism spectrum disorder: current status and possible clinical applications. Exp Neurobiol 2015;24:257.
36. Ross JL, Roeltgen DP, Kushner H, et al. Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY klinefelter syndrome. Pediatrics 2012;129:769-78.
37. Bardsley MZ, Kowal K, Levy C, et al. 47,XYY syndrome: clinical phenotype and timing of ascertainment. J Pediatr 2013;163:1085-94.
38. Durkin MS, Maenner MJ, Newschaffer CJ, et al. Advanced parental age and the risk of autism spectrum disorder. Am J Epidemiol 2008;168:1268-76.
39. Agrawal S, Rao SC, Bulsara MK, et al. Prevalence of autism spectrum disorder in preterm infants: a metaanalysis. Pediatrics 2018;142:e20180134.
40. Wang C, Geng H, Liu W, et al. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. Medicine (Baltimore) 2017;96:e6696.
41. Parner ET, Baron-Cohen S, Lauritsen MB, et al. Parental age and autism spectrum disorders. Ann Epidemiol 2012;22:143-50.
42. Buie T, Campbell DB, Fuchs GJ III, Furuta GT, Levy J, et al. 2010. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics 125(Suppl. 1):S1–18
43. Chaidez V, Hansen RL, Hertz-Picciotto I. 2013. Gastrointestinal problems in children with autism, developmental delays or typical development. J. Autism Dev. Disord. 44(5):1117–27
44. Chen JA, Penagarikano O, Belgard TG, Swarup V, Geschwind DH. 2015. The emerging picture of autism spectrum disorder: genetics and pathology. Annu. Rev. Pathol. 10:111–44
45. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, et al. 2014. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol. Psychiatry 19:659–67
46. Lefebvre A, Beggiato A, Bourgeron T, Toro R. 2015. Neuroanatomical diversity of corpus callosum and brain volume in autism: meta-analysis, analysis of the autism brain imaging data exchange project, and simulation. Biol. Psychiatry 78:126–34
47. Rossignol DA, Frye RE. 2012. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol. Psychiatry 17:290–314
48. Sacco R, Gabriele S, Persico AM. 2015. Head circumference and brain size in autism spectrum disorder: a systematic review and meta-analysis. Psychiatry Res. 234:239–51
49. Tuchman R, Rapin I. Epilepsy in autism. Lancet Neurol. 2002;1(6):352–8
50. Hara H. Autism and epilepsy: a retrospective follow-up study. Brain Dev. 2007;29(8):486–90.
51. Blackmon K, Bluvstein J, MacAllister WS, et al. Treatment resistant epilepsy in autism spectrum disorder: increased risk for females. Autism Res. 2016;9(2): 311–20.
52. Sansa G, Carlson C, Doyle W, et al. Medically refractory epilepsy in autism. Epilepsia. 2011;52(6):1071–5.
53. Amiet C, Gourfinkel-An I, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry. 2008;64(7):577–82.
54. El Achkar CM, Spence SJ. Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. Epilepsy Behav. 2015;47:183–90.
55. Pickett J, Xiu E, Tuchman R, Dawson G, Lajonchere C. Mortality in individuals with autism, with and without epilepsy. J Child Neurol. 2011;26(8):932–9.
56. Shavelle RM, Strauss DJ, Pickett J. Causes of death in autism. J Autism Dev Disord. 2001;31(6):569–76.

57. Jabbari K, Nurnberg P. A genomic view on epilepsy and autism candidate genes. Genomics. 2016. [In press].
58. Lee BH, Smith T, Paciorkowski AR. Autism spectrum disorder and epilepsy: disorders with a shared biology. Epilepsy Behav. 2015;47:191–201.
59. Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. Epilepsy Behav. 2015;47:147–57.
60. Frye RE, Rossignol D, Casanova MF, et al. A review of traditional and novel treatments for seizures in autism spectrum disorder: findings from a systematic review and expert panel. Front Public Health. 2013;1:31.
61. Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. Epilepsy Behav. 2006;8(1):267–71. 52. Munoz-Yunta JA, Ortiz T, Palau-Baduell M, et al. Magnetoencephalographic pattern of epileptiform activity in children with early-onset autism spectrum disorders. Clin Neurophysiol. 2008;119(3):626–34.
62. Parmeggiani A, Barcia G, Posar A, Raimondi E, Santucci M, Scaduto MC. Epilepsy and EEG paroxysmal abnormalities in autism spectrum disorders. Brain Dev. 2010;32(9):783–9.
63. Oslejskova H, Dusek L, Makovska Z, Pejcochova J, Autrata R, Slapak I. Complicated relationship between autism with regression and epilepsy. Neuro Endocrinol Lett. 2008;29(4):558–70.
64. Frye RE, Butler I, Strickland D, Castillo E, Papanicolaou A. Electroencephalogram discharges in atypical cognitive development. J Child Neurol. 2010;25(5):556–66.
65. Frye RE. Prevalence, significance and clinical characteristics of seizures, epilepsy and subclinical electrical activity in autism. N Am J Med Sci. 2015;8(3):113–22.
66. Hartley-McAndrew M, Weinstock A. Autism spectrum disorder: correlation between aberrant behaviors, EEG abnormalities and seizures. Neurol Int. 2010; 2(1): e10
67. rye RE, James SJ. Metabolic pathology of autism in relation to redox metabolism. Biomark Med. 2014;8(3):321–30.
68. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: systematic review and meta-analysis. Mol Psychiatry. 2012;17(3):290–314.
69. Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. Epilepsy Behav. 2015;47:147–57.
70. Rossignol DA, Frye RE. The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review. Front Pediatr. 2014;2:87.
71. Oberman LM. mGluR antagonists and GABA agonists as novel pharmacological agents for the treatment of autism spectrum disorders. Expert Opin Investig Drugs. 2012;21(12):1819–25
72. Maloney SE, Rieger MA, Dougherty JD. Identifying essential cell types and circuits in autism spectrum disorders. Int Rev Neurobiol. 2013;113:61–96.
73. Frye RE. Clinical potential, safety, and tolerability of arbaclofen in the treatment of autism spectrum disorder. Drug Healthc Patient Saf. 2014;6:69–76.
74. Frye RE, Rossignol DA. Treatments for biomedical abnormalities associated with autism spectrum disorder. Front Pediatr. 2014;2:66.
75. Rose S, Melnyk S, Pavliv O, et al. Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. Transl Psychiatry. 2012;2:e134.
76. Rossignol DA, Frye RE. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Front Physiol. 2014;5:150.
77. Deepmala, Slattery J, Kumar N, et al. Clinical trials of N-acetylcysteine in psychiatry and neurology: a systematic review. Neurosci Biobehav Rev. 2015;55:294–321.
78. Lefevre A, Sirigu A. The two fold role of oxytocin in social developmental disorders: a cause and a remedy? Neurosci Biobehav Rev. 2016;63:168–76.
79. Klukowski M, Wasilewska J, Lebensztejn D. Sleep and gastrointestinal disturbances in autism spectrum disorder in children. Dev Period Med. 2015;19(2):157–61.
80. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders. Curr Clin Pharmacol. 2014;9(4):326–34.
81. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 2011;53(9):783–92.
82. Nadeau JM, Arnold EB, Keene AC, et al. Frequency and clinical correlates of sleep-related problems among anxious youth with autism spectrum disorders. Child Psychiatry Hum Dev. 2015;46(4):558–66.
83. Hill AP, Zuckerman KE, Hagen AD, et al. Aggressive behavior problems in children with autism spectrum disorders: prevalence and correlates in a large clinical sample. Res Autism Spectr Disord. 2014;8(9):1121–33.
84. Tilford JM, Payakachat N, Kuhlthau KA, et al. Treatment for sleep problems in children with autism and caregiver spillover effects. J Autism Dev Disord. 2015;45(11):3613–23.
85. Tordjman S, Anderson GM, Bellissant E, et al. Day and nighttime excretion of 6-sulphatoxymelatonin in adolescents and young adults with autistic disorder. Psychoneuroendocrinology. 2012;37(12):1990–7.
86. Tordjman S, Anderson GM, Pichard N, Charbuy H, Touitou Y. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. Biol Psychiatry. 2005;57(2):134–8.
87. Leu RM, Beyderman L, Botzolakis EJ, Surdyka K, Wang L, Malow BA. Relation of melatonin to sleep architecture in children with autism. J Autism Dev Disord. 2011;41(4):427–33.
88. Pagan C, Delorme R, Callebert J, et al. The serotonin-N-acetylserotoninmelatonin pathway as a biomarker for autism spectrum disorders. Transl Psychiatry. 2014;4:e479.
89. Melke J, Goubran Botros H, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. Mol Psychiatry. 2008;13(1):90–8.
90. Frye RE, Rossignol D. Mitochondrial and metabolic abnormalities in neurodevelopmental disorders. J Pediatr Biochem. 2012;4(2):177–80.
91. Obeid R, McCaddon A, Herrmann W. The role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric diseases. Clin Chem Lab Med. 2007;45(12):1590–606.

92. Frustaci A, Neri M, Cesario A, et al. Oxidative stress-related biomarkers in autism: systematic review and meta-analyses. Free Radic Biol Med. 2012;52(10): 2128–41
93. Boris M, Goldblatt A, Galanko J, James SJ. Association of MTHFR gene variants with autism. J Am Phys Surg. 2004;9(4):106–8.
94. Mohammad NS, Jain JM, Chintakindi KP, Singh RP, Naik U, Akella RR. Aberrations in folate metabolic pathway and altered susceptibility to autism. Psychiatr Genet. 2009;19(4):171–6.
95. Guo T, Chen H, Liu B, Ji W, Yang C. Methylenetetrahydrofolate reductase polymorphisms C677T and risk of autism in the Chinese Han population. Genet Test Mol Biomarkers. 2012;16(8):968–73.
96. Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) casecontrol study. Am J Clin Nutr. 2012;96(1):80–9.
97. Liu X, Solehdin F, Cohen IL, et al. Population- and family-based studies associate the MTHFR gene with idiopathic autism in simplex families. J Autism Dev Disord. 2011;41(7):938–44.
98. Goin-Kochel RP, Porter AE, Peters SU, Shinawi M, Sahoo T, Beaudet AL. The MTHFR 677C--.T polymorphism and behaviors in children with autism: exploratory genotype-phenotype correlations. Autism Res. 2009;2(2): 98–108.
99. Pasca SP, Dronca E, Kaucsar T, et al. One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders. J Cell Mol Med. 2009;13(10):4229–38.
100. James SJ, Melnyk S, Jernigan S, et al. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet B Neuropsychiatr Genet. 2006;141B(8):947–56.
101. Pu D, Shen Y, Wu J. Association between MTHFR gene polymorphisms and the risk of autism spectrum disorders: a meta-analysis. Autism Res. 2013;6(5):384–92.
102. Adams M, Lucock M, Stuart J, Fardell S, Baker K, Ng X. Preliminary evidence for involvement of the folate gene polymorphism 19 bp deletion-DHFR in occurrence of autism. Neurosci Lett. 2007;422(1):24–9.
103. Frye RE, Naviaux RK. Autistic disorder with complex IV overactivity: a new mitochondrial syndrome. J Pediatr Neurol. 2011;9(4):427–34.
104. Ramaekers VT, Quadros EV, Sequeira JM. Role of folate receptor autoantibodies in infantile autism. Mol Psychiatry. 2013;18(3):270–1.
105. Frye RE. Central tetrahydrobiopterin concentration in neurodevelopmental disorders. Front Neurosci. 2010;4:52.
106. Frye RE, Huffman LC, Elliott GR. Tetrahydrobiopterin as a novel therapeutic intervention for autism. Neurotherapeutics. 2010;7(3):241–9.
107. Frye RE, Melnyk S, Macfabe DF. Unique acyl-carnitine profiles are potential biomarkers for acquired mitochondrial disease in autism spectrum disorder. Transl Psychiatry. 2013;3:e220.
108. Filipek PA, Juranek J, Nguyen MT, Cummings C, Gargus JJ. Relative carnitine deficiency in autism. J Autism Dev Disord. 2004;34(6):615–23.
109. Celestino-Soper PB, Violante S, Crawford EL, et al. A common X-linked inborn error of carnitine biosynthesis may be a risk factor for nondysmorphic autism. Proc Natl Acad Sci U S A. 2012;109(21):7974–81.
110. Zhang Y, Hodgson NW, Trivedi MS, et al. Decreased brain levels of vitamin B12 in aging, autism and schizophrenia. PLoS One. 2016;11(1):e0146797.
111. Clark-Taylor T, Clark-Taylor BE. Is autism a disorder of fatty acid metabolism? Possible dysfunction of mitochondrial beta-oxidation by long chain acyl-CoA dehydrogenase. Med Hypotheses. 2004;62(6):970–5.
112. Macfabe DF. Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders. Microb Ecol Health Dis. 2012;23:19260
113. Foley KA, MacFabe DF, Kavaliers M, Ossenkopp KP. Sexually dimorphic effects of prenatal exposure to lipopolysaccharide, and prenatal and postnatal exposure to propionic acid, on acoustic startle response and prepulse inhibition in adolescent rats: relevance to autism spectrum disorders. Behav Brain Res. 2015;278:244–56.
114. Foley KA, Ossenkopp KP, Kavaliers M, Macfabe DF. Pre- and neonatal exposure to lipopolysaccharide or the enteric metabolite, propionic acid, alters development and behavior in adolescent rats in a sexually dimorphic manner. PLoS One. 2014;9(1):e87072
115. Buie T, Fuchs GJ III, Furuta GT, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics. 2010;125(suppl 1):S19–29.
116. Buie T, Campbell DB, Fuchs GJ III, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 2010;125(suppl 1):S1–18.
117. Bresnahan M, Hornig M, Schultz AF, et al. Association of maternal report of infant and toddler gastrointestinal symptoms with autism: evidence from a prospective birth cohort. JAMA Psychiatry. 2015;72(5):466–74.
118. Williams BL, Hornig M, Buie T, et al. Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS One. 2011;6(9):e24585.
119. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics 2007;120:1183-215.
120. Agrawal S, Rao SC, Bulsara MK, et al. Prevalence of autism spectrum disorder in preterm infants: a metaanalysis. Pediatrics 2018;142:e20180134.
121. Skefos J, Cummings C, Enzer K, et al. Regional alterations in Purkinje cell density in patients with autism. PLoS One 2014;9:e81255
122. Stoodley CJ, D'Mello AM, Ellegood J, et al. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat Neurosci 2017;20:1744-51.
123. De Rubeis S, He X, Goldberg AP, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014;515:209-15.
124. Shen MD, Kim SH, McKinstry RC, et al. Increased extraaxial cerebrospinal fluid in high-risk infants who later develop autism. Biol Psychiatry 2017;82:186-93.
125. Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum disorder. Nature 2017;542:348-51.
126. Kim H, Keifer C, Rodriguez-Seijas C, et al. Quantifying the optimal structure of the autism phenotype: a comprehensive comparison of dimensional, categorical, and hybrid models. J Am Acad Child Adolesc Psychiatry 2019;58:876-86.e2.
127. Sandin S, Lichtenstein P, Kuja-Halkola R, et al. The familial risk of autism. JAMA 2014;311:1770-7.

128. Risch N, Hoffmann TJ, Anderson M, et al. Familial recurrence of autism spectrum disorder: Evaluating genetic and environmental contributions. Am J Psychiatry 2014;171:1206-13.
129. Walsh CA, Morrow EM, Rubenstein JLR. Autism and brain development. Cell 2008;135:396-400.
130. Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2003;2:255-67.
131. McDougle CJ, Erickson CA, Stigler KA, et al. Neurochemistry in the pathophysiology of autism. J Clin Psychiatry 2005;66 Suppl 10:9-18.
132. Veenstra-Vanderweele J, Christian SL, Cook EH Jr. Autism as a paradigmatic complex genetic disorder. Annu Rev Genomics Hum Genet 2004;5:379-405.
133. Surén P, Roth C, Bresnahan M, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA 2013;309:570-7.
134. Bjørk M, Riedel B, Spigset O, et al. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. JAMA Neurol 2018;75:160.
135. Rasalam AD, Hailey H, Williams JHG, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005;47:551-5.
136. Frye RE, Slattery J, Delhey L, et al. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebocontrolled trial. Mol Psychiatry 2018;23:247-56.
137. Croen LA, Najjar DV, Fireman B, et al. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med 2007;161:334-40.
138. Xiang AH, Wang X, Martinez MP, et al. Maternal type 1 diabetes and risk of autism in offspring. JAMA 2018;320:89-91.
139. Croen LA, Grether JK, Yoshida CK, et al. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med 2005;159:151-7.
140. Malkova NV, Yu CZ, Hsiao EY, et al. Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. Brain Behav Immun 2012;26:607-16.
141. Estes ML, McAllister AK. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat Rev Neurosci 2015;16:469-86.
142. Choi GB, Yim YS, Wong H, et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 2016;351:933-9.
143. Croen LA, Qian Y, Ashwood P, et al. Infection and fever in pregnancy and autism spectrum disorders: findings from the study to explore early development. Autism Res 2019. [Epub ahead of print].
144. Schieve LA, Tian LH, Drews-Botsch C, et al. Autism spectrum disorder and birth spacing: findings from the study to explore early development (SEED). Autism Res 2018;11:81-94
145. Newschaffer CJ, Croen LA, Daniels J, et al. The epidemiology of autism spectrum disorders. Annu Rev Public Health 2007;28:235-58
146. Ruzzo EK, Pérez-Cano L, Jung JY, et al. Inherited and de novo genetic risk for autism impacts shared networks. Cell 2019;178:850-66.e26.
147. Vllasaliu, L., Jensen, K., Hoss, S., Landenberger, M., Menze, M., Schütz, M., Ufniarz, K., Kieser, M. and Freitag, C.M., 2016. Diagnostic instruments for autism spectrum disorder (ASD). Cochrane Database of Systematic Reviews, (1).
148. Skuse, D., Warrington, R., Bishop, D., Chowdhury, U., Lau, J., Mandy, W., & Place, M. (2004).The developmental, dimensional and diagnostic interview (3di): A novel computerized assessment for autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry 43(5), 548–558.
149. Schopler, E., Reichler, R. J., DeVellis, R. F., & Daly, K. (1980). Toward objective classification of childhood autism: Childhood autism rating scale (CARS). Journal of Autism and Developmental Disorders 10(1), 91–103
150. Neal, D., Matson, J. L., & Hattier, M. A. (2014). Validity of the Autism Spectrum Disorder Observation for Children (ASD-OC). Journal of Mental Health Research in Intellectual Disabilities 7(1), 14–33.
151. Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders 24(5), 659–685
152. Gillberg, C., Gillberg, C., Råstam, M., & Wentz, E. (2001). The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI): A preliminary study of a new structured clinical interview. Autism 5(1), 57–66.
153. Maljaars, J., Noens, I., Scholte, E., & van Berckelaer-Onnes, I. (2012). Evaluation of the criterion and convergent validity of the diagnostic interview for social and communication disorders in young and low-functioning children. Autism 16(5), 487–497.
154. Matson, J. L., Wilkins, J., Boisjoli, J. A., & Smith, K. R. (2008). The validity of the autism spectrum disorders-diagnosis for intellectually disabled adults (ASD-DA). Research in Developmental Disabilities 29(6), 537–546.
155. Aman, M. G., Farmer, C. A., Hollway, J., & Arnold, L. E. (2008). Treatment of inattention, overactivity, and impulsiveness in autism spectrum disorders. Child and Adolescent Psychiatric Clinics of North America 17(4), 713–738.
156. Davis, N. O., & Kollins, S. H. (2012). Treatment for co-occurring attention deficit/hyperactivity disorder and autism spectrum disorder. Neurotherapeutics 9(3), 518–530
157. Handen, B. L., Johnson, C. R., & Lubetsky, M. (2000). Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. Journal of Autism and Developmental Disorders 30, 245–255
158. Baldessarini, R. J., & Tarazi, F. I. (2005). Pharmacotherapy of psychosis and mania. In L. L. Brunton, J. S. Lazo, & K. L. Parker (Eds.), Goodman and Gilman's the pharmacological basis of therapeutics (pp. 461–500). New York, NY: McGraw-Hill.
159. Posey, D. J., Stigler, K. A., Erickson, C. A., & McDougle, C. J. (2008). Antipsycohtics in the treatment of autism. The Journal of Clinical Investigation 118(1), 6–14
160. Langworthy-Lam, K. S., Aman, M. G., & van Bourgondien, M. E. (2002). Prevalence and patterns of use of psychoactive medicines in individuals with autism in the Autism Society of North Carolina. Journal of Child and Adolescent Psychopharmacology 12, 311–321

161. Nadeau, J., Sulkowski, M. L., Ung, D., Wood, J. J., Lewin, A. B., Murphy, T. K., ... Storch, E. A. (2011). Treatment of comorbid anxiety and autism spectrum disorders. Neuropsychiatry 1(6), 567–578
162. Newcorn, J. H., Schulz, K., Harrison, M., DeBellis, M. D., Udarbe, J. K., & Halperin, J. M. (1998). Alpha 2 adrenergic agonists. Neurochemistry, efficacy, and clinical guidelines for use in children. Pediatric Clinics of North America 45(5) (1099-1022)
163. Fankhauser, M. P., Karumanchi, V. C., German, M. L., Yates, A., & Karumanchi, S. D. (1992). A double-blind placebo-controlled study of the efficacy of transdermal clonidine in autism. The Journal of Clinical Psychiatry 53(3), 77–82
164. Scahill, L., McCracken, J. T., King, B. H., Rockhill, C., Shah, B., Politte, L., ... Research Units on Pediatric Psychopharmacology Autism Network (2015). Extended-eelease guanfacine for hyperactivity in children with autism spectrum disorder. The American Journal of Psychiatry 172(12), 1197–1206
165. Handen, B. L., Sahl, R., & Hardan, A. Y. (2008). Guanfacine in children with autism and/or intellectual disabilities. Journal of Developmental and Behavioral Pediatrics 29(4), 303–308.
166. Reichow, B., Barton, E. E., Boyd, B. A., & Hume, K. (2012). Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews 10, CD009260.
167. Hanson, E., Kalish, L. A., Bunce, E., Curtis, C., McDaniel, S., Ware, J., & Petry, J. (2007). Use of complementary and alternative medicine among children diagnosed with autism spectrum disorder. Journal of Autism and Developmental Disorders 37(4), 628–636.
168. Brondino, N., Fusar-Poli, L., Rocchetti, M., Provenzani, U., Barale, F., & Politi, P. (2015). Complementary and alternative therapies for autism spectrum disorder. Evidencebased Complementary and Alternative Medicine 2015, 258589.
169. Altenmüller, E., & Schlaug, G. (2015). Apollo's gift: New aspects of neurologic music therapy. Progress in Brain Research 217, 237–252.
170. Heaton, P. (2009). Assessing musical skills in autistic children who are not savants. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 364(1522), 1443–1447.
171. Sharda, M., Midha, R., Malik, S., Mukerji, S., & Singh, N. C. (2015). Fronto-temporal connectivity is preserved during sung but not spoken word listening, across the autism spectrum. Autism Research 8(2), 174–186
172. Hesselmark, E., Plenty, S., & Bejerot, S. (2014). Group cognitive behavioural therapy and group recreational activity for adults with autism spectrum disorders: A preliminary randomized controlled trial. Autism 18, 672–683
173. Ung, D., Selles, R., Small, B. J., & Storch, E. A. (2015). A systematic review and meta-analysis of cognitive-behavioral therapy for anxiety in youth with high-functioning autism spectrum disorders. Child Psychiatry and Human Development 46, 533–547.
174. Danial, J. T., & Wood, J. J. (2013). Cognitive behavioral therapy for children with autism: Review and considerations for future research. Journal of Developmental and Behavioral Pediatrics 34, 702–715
175. Lai, M. -C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. Lancet 383, 896–910
176. Vismara, L. A., & Rogers, S. J. (2010). Behavioral treatments in autism spectrum disorder: What do we know? Annual Review of Clinical Psychology 6, 447–468.
177. Bahmani, M., Sarrafchi, A., Shirzad, H., & Rafieian-Kopaei, M. (2016). Autism: Pathophysiology and promising herbal remedies. Current Pharmaceutical Design 22, 277–285.
178. Bang, M., Lee, S. H., Cho, S. H., Yu, S. A., Kim, K., Lu, H. Y., ... Min, S. Y. (2017). Herbal medicine treatment for children with autism spectrum disorder: A systematic review. Evidence-based Complementary and Alternative Medicine 8614680.