Review Article: The Autism Disease: Symptoms, Genomics, Causes and Pharmacological Therapy for the Behavioral associated with disease

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ABSTRACT
One of the most confusing conditions is autism spectrum disorders (ASDs), for which neither a precise cause nor a conclusive cure has yet been discovered. Autism can be defined as a disorder that typically manifests in children at a young age and affects many areas of their development. It develops in an abnormal way, exhibiting an unbalanced social interaction style marked by recurring behavioral patterns and difficulties in verbal and nonverbal communication. The frequency of ASDs has dramatically increased over the past few decades, inspiring numerous researchers worldwide to investigate all facets of the condition, from origin to intervention and diagnosis. This study addresses ASDs, their causes, symptoms, diagnosis, modalities of therapy, and the counseling needs of Jordanian families. As one of the most common neurodevelopmental disorders, ASDs are characterized by stereotyped behaviors and poor social interaction. There is a significant and intricate genetic component to ASDs, with numerous patterns of familial inheritance and an estimated 1,000 potential genes. The past ten years have seen a rapid advancement in identifying the genes responsible for autism, thanks to genomic technologies. This study describes pharmaceutical treatments for the behavioral symptoms associated with ASDs in adolescents, children, and adults. The categories of symptoms include inattention and hyperactivity, social impairment, aggression, irritability, and stereotyped and repetitive behaviors. Medications covered in the list include α-2 agonists, atomoxetine, mirtazapine, memantine, serotonin reuptake inhibitors (SRIs), and antipsychotics. In children with ASDs, SRIs are generally less effective and less tolerated compared to adults. The most effective medications for treating irritability in ASDs are antipsychotics, which can also help with other symptoms. While psychostimulants show promise when used to treat inattention and hyperactivity in individuals with ASDs, they are less effective and have more side effects compared to their use in individuals with attention deficit and hyperactivity disorders (ADHDs). Although more research is needed, memantine and D-cycloserine appear to be beneficial in treating social impairment.

1. Introduction

Due to starting before the age of three and causing problems and delays in a wide range of skills from childhood to adulthood, ASDs are often referred to as developmental disabilities[1]. ASDs can be defined as complex neurobiological developmental disorders that persist throughout a person's life. The symptoms of autism include repetitive behaviors, poor communication and social skills, neurological disorders such as ADHD and schizophrenia, medical conditions like congenital malformations and digestive system issues, as well as neurological disorders like sleep disorders, motor deficits, and epilepsy. Despite being highly varied, disturbances are common in ASDs[2]. These disorders are caused by a complex genetic diversity, genetic patterns, and specific genomic loci[3]. Recent research has shown that all genes contribute to autism risk factors, and ongoing investigations are exploring the role of common analyses that link an organism's phenotype and genotype. There are numerous types of genetic variations with different frequencies (rare, common, and extremely rare variations). Examples of autosomal and X-linked de novo variations include Copy Number Variation (CNV), Aneuploidy, and Single Nucleotide Variation[4]. When considering a single nucleotide polymorphism (SNP), common variant SNPs have little effect. Consequently, research has shown that the weak influence of individual SNPs has so far resulted in a weak genome-wide connection. On the contrary, the genetic risk associated with a large number of single nucleotide polymorphisms is significant. One important factor influencing the variability of ASDs is SNPs[5].

Autism Symptoms

We can list several symptoms indicated by the child's behavior[6]:

1. The child consistently tries to isolate themselves from those around them.

2. Their conversations are not with peers of the same age. Furthermore, they may lose many friends if they do, making it challenging for them to maintain friendships.

3. Both understanding their own emotions and recognizing the emotional states of others present challenges for them. Children with autism may struggle to identify gestures, facial expressions, and vocal tones.

4. They face difficulties with both non-verbal and verbal communication. Some individuals may never learn to develop any language skills.

5. Language and speech-related disorders.

6. Challenges in social relationships.

7. Engaging in a stereotypical, repetitive pattern of interests and behaviors.

8. Difficulty in establishing relationships with peers (lack of friendships, extreme disinterest in peers) and an inability to regulate social interactions through nonverbal cues (such as imitation, social smiling, and eye contact).

9. Difficulty expressing emotions to others.

10. Lack of social-emotional connections with others (lack of emotional responses, inappropriate social behaviors, absence of comforting reactions).

11. Speech that may appear incomprehensible or unclear to others.

12. Engaging in repetitive and stereotyped actions, such as verbalizing thoughts aloud.

13. Unusual routines or highly specific narrow interests (such as finger twisting in front of the eyes, fixed rituals of observing moving objects, bouncing, or rocking a chair) are examples of repetitive behaviors.

14. Fixation on parts of objects or non-functional items (e.g., wheelchairs, doll eyes) or an unusual fascination with sensory characteristics (e.g., fixation on specific tastes, scents, or textures).

Autism Causes:

According to certain studies, the history of the condition is influenced by the active substance as well as environmental factors. In terms of genetics, it has been established that while one of the identical twins shares the same genetic code as the other, they were diagnosed with autism[7]. In addition to environmental factors, many experts in the field base their research on the interaction that occurs between multiple gene groups. We will identify characteristics that increase the likelihood of autism in children and examine the environmental factors associated with this condition to gain a broader understanding of these elements[8]. First, let's define what the term "environment" means in the context of medicine. Water, air, food, and even medications are all considered parts of the environment, which encompasses everything outside the human body that has the ability to impact a person's health. Some scientists focused on studying specific environmental factors, including exposure, parental age, and family medical history[8]. An increased risk of autism is associated with various factors, including exposure to hazardous substances during pregnancy and potential complications during or after childbirth. However, a large number of individuals exposed to environmental risk factors do not show symptoms indicative of ASDs[9].

ASDs genes Identification:

ASDs represent complex genetic disorders. Genetic factors that can be identified include specific gene mutations that appear to result in ASDs on their own (with or without other related conditions), chromosomal abnormalities, and susceptibility loci that do not necessarily lead to ASDs[10], as illustrated in Figure 1. It is now believed that genetic variation accounts for a small percentage of

ASDs, while the majority are caused by the interaction of numerous susceptibility loci[11].

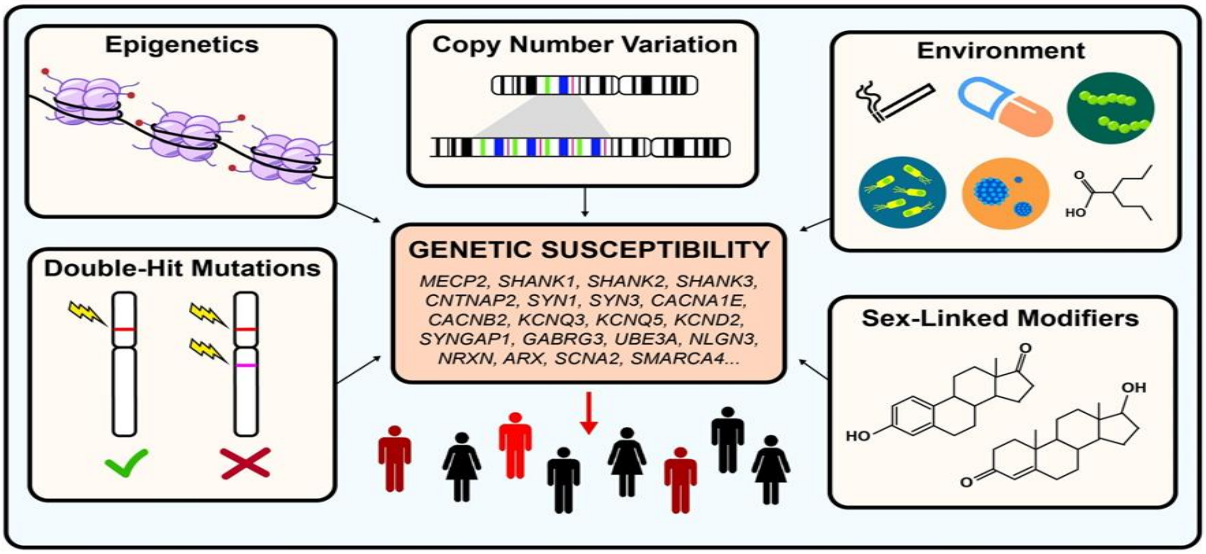

FIGURE 1. Genetic modifiers in autism spectrum disorder. Autism is estimated to be 40–80% heritable. However, both genetic and non-genetic factors modulate the penetrance of risk genes, resulting in a highly heterogeneous disease phenotype for similar pathogenic variants. Examples of genetic modulators include CNV, epigenetics, and double-hit mutations. Examples of non-genetic modifiers include environmental exposures and sex-linked modifiers.

Causal Genetic Variation:

Numerous genes associated with specific chromosomal abnormalities related to autism have been linked to abnormal chromosomes and specific fetal mutations that contribute significantly to ASDs. The most common of these mutations are chromosomal duplications or deletions in the 15q11 region, known as Prader-Willi syndrome, Angelman syndrome, 22q13 deletion syndrome, and Down syndrome (recently associated with a single SHANK3/PROSAP2 gene defect), as well as other less common conditions and disorders such as fragile X syndrome. This gene includes the DHCR7 gene and Rett syndrome caused by mutations in the MECP2 gene, as well as Smith-Lemli-Opitz syndrome[12]. Among the genetic factors that lead to autism syndrome are:

5.1. Engrailed 2/ Chromosome 7: On chromosome 7, the transcription factor Engrailed2 (EN2) plays a role in the cerebellar development. Autism syndrome disorders (ASDs) is brought on by disruption of such gene, which also leads to certain cerebellar malformation[13].

5.2. AGC_1 / SLC_{25} A_{12} / Chromosome 2: This gene is located on chromosome 2 in humans, and several studies have linked it to ASDs[14]. This gene plays a role in mitochondrial function, helping to maintain stable ATP energy levels within the cell[15]. It was later discovered that the gene also plays a role in the myelination process. A decrease in nerve connectivity due to myelination could explain some of the behavioral observations in individuals with ASDs[16].

5.3. Chromosome 2: Researchers have discovered that specific areas of chromosome 2 correspond to the homebox, or Hox, genes—a family of genes that regulates growth and development from an early age, the cerebellum and brainstem are two areas of the cerebellum and brain where the expression of Hox genes is essential for their development. When ASD affects these areas, their functions are disrupted[17].

5.4. Chromosome 7: Researchers have discovered a strong correlation between this chromosome and autism. Studies are concentrated on a region known as AuTS1, which is likely associated with autism[18]. As ASDs affect these functions, there is evidence linking the region of chromosome 7 to language and speech disorders. The majority of genomic research indicates that AuTS1 plays a role

in autism[19].

5.5. Chromosome 13: Research indicates that the region of chromosome 13 may be linked to autism disorder in approximately 35% of the families that were investigated[19].

5.6. Chromosome 15: According to cytogenetic research, a segment of this chromosome may be implicated in autism, as genomic errors in this chromosome can lead to both Parder-Willi syndrome and Angelman syndrome, both of which manifest autism-like behaviors and symptoms. Genetic errors on chromosome 15 can occur at a rate of 4%[16].

5.7. Chromosome 16: The genes on this chromosome control various functions that, when disturbed, can lead to issues resembling or linked to symptoms of autism. Certain regions on the chromosome could be associated with conditions such as Tuberous Sclerosis, which is triggered by a genetic mutation and shared among several autism spectrum disorders. In terms of specific behavioral aspects[20].

5.8. Chromosome 17: The chromosome contains genes that, when malfunctioning or missing, can lead to various issues, including galactosemia, a metabolic disorder that can cause mental impairment if left untreated[20]. Furthermore, chromosome 17 houses the distinctive serotonin transporter gene, responsible for allowing nerve cells to absorb serotonin. Serotonin plays a role in regulating emotions and nerve cell communication. Problems with the serotonin transporter may be a contributing factor to the development of obsessive-compulsive disorder (OCD), characterized by repetitive and intrusive thoughts[21].

5.9. Chromosome X: Genes on the X chromosome are typically associated with two disorders that share symptoms with autism: Fragile X Syndrome and Rett Syndrome. This implies that genes on the X chromosome may play a role in the development of disorders related to autism[21]. Most cells in a person's body contain 46 chromosomes, with 23 inherited from the father and 23 from the mother. These chromosomes pair up to form 23 pairs of chromosomes following fertilization, with the 23rd pair designated as the sex chromosomes (X, Y)[20]. Studies suggest that there is a higher incidence of autism in males compared to females, supporting the idea that genes on the X chromosome contribute to the disorder. While females may be able to compensate for X chromosome and other functions normally, males may not[22].

5.10. The Reelin gene / Chromosome 7: The Reelin gene is a strong candidate as it plays a role in the development of connections between cells in the nervous system, and abnormal connections in the brain are known to be a contributing factor to autism[23]. Specific forms of the Reelin protein are expressed at lower levels in individuals with autism, pointing to abnormal gene function[24].

5.11. $HoxD_1$ gene: This homologous gene plays a role in the development of the brain's structure and is associated with Duane Syndrome, an eye movement abnormality that can sometimes occur alongside autism[25]. In a study on autism, approximately 94% of patients were found to have multiple mutations in the HoxD1 gene, suggesting that this region is involved in conditions related to autism spectrum disorders[26].

5.12. Gama Amino Butyric Acid Pathway (GABA): As neurotransmitters, GABA compounds facilitate communication between different components of the nervous system. GABA receptor genes support communication throughout life and are involved in the early development of specific nervous system components. Issues within the GABA pathway could underlie certain symptoms of ASDs. For example, epilepsy can lead to decreased levels of GABA compounds, and some individuals with autism exhibit low GABA level[27].

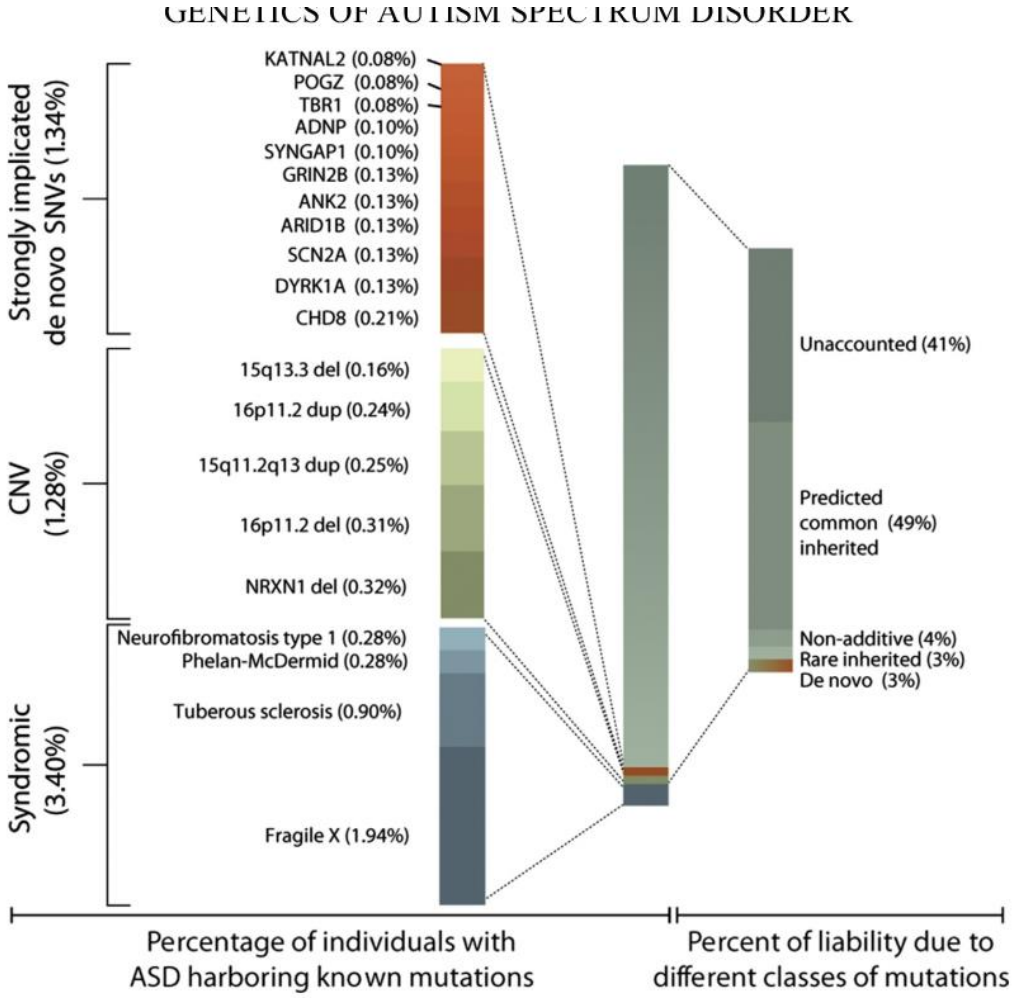

FIGURE 2. Genetic contributions to the population of individuals with Autism Spectrum Disorders (ASDs). The percentage of individuals with ASDs carrying known mutations, as well as the percentage of liability from different classes of mutations, are derived from Gaugler *et al.* (2014)[24]. The percentage of variance in liability measures the contribution of a specific variant or class of variants in relation to the overall population variance in a theoretical variable known as liability. Liability is a continuous and normally distributed latent variable that represents each individual's risk (both genetic and environmental) of developing a disease. (Adapted from de la Torre-Ubieta *et al.*[25] Advancing the understanding of autism disease mechanisms through genetics. Nat Med 22: 345–361).

5.13. Serotonin Transport gene / Chromosome 17: The neurotransmitter serotonin has been associated with several disorders, such as obsessive-compulsive disorder, depression, alcoholism, and others[29]. Studies have shown that individuals with autism tend to have higher levels of serotonin (25–50%) compared to those without autism. This increased serotonin level could be linked to genetic errors[28]. As shown in Figure 2.

Genotype – Phenotype Relationships:

Considerable genetic overlap has been identified in studies linking Autism Spectrum Disorders (ASDs) to other neurodevelopmental disorders, such as intellectual disability (ID) and schizophrenia[27]. Research has shown comprehensive clinical characterization of a group of patients with a common etiology exhibiting significant variation in gene expression related to duplicate genes and mutations, revealing shared genes and pathways between congenital heart disease (CHD) and ASDs using a genotype-first approach[28]. Examples of this overlap include the deletions of 22q11.2 and 16p11.2. The varying severity of several neuropsychiatric disorders, such as ASDs and

schizophrenia, is associated with these two deletions. Additionally, these deletions can be identified in healthy individuals, indicating incomplete penetrance[25].

Interventions:

As of yet, no medication was discovered that can be used for treating autism. Nonetheless, a variety of treatments are available to try to enhance these children with autism's quality of life [25]:

7.1. Behavioral Therapy: Also referred to as Skinner or Lovaas, it is founded on behaviorism and promotes children's skill development through a system of rewards and penalties[29].

7.2. Teach Methods: This approach, which emphasizes communication through images, was utilized in a few educational facilities, primarily in Missouri and Texas[30].

7.3. Picture Exchange Communication System (PECS): A method of learning writing and reading through visual components. Great success has been achieved with the application in the US and other nations[31].

7.4. Chemical / Drug: Until you have a prescription, it is undeniable that certain children with autism require medications[32].

7.5. Diet: A diet free of gluten and casein involves restricting the consumption of foods high in gluten or casein, which are commonly found in products like wheat flour and dairy. While this dietary approach is beneficial in only a limited number of cases and has no known adverse effects, it is still considered a potential alternative[30].

7.6. Vitamins: It entails giving the child a range of vitamins to make up for any deficiencies. Research has shown that certain children with autism do not receive enough vitamins, including vitamin B-complex[32].

Pharmacological treatment for the behavioral:

Behavioral symptoms associated with autism include aggression, irritability, inattention, hyperactivity, stereotyped and repetitive behaviors, and social impairment. Additionally, stereotypical motor patterns like clapping, flapping, rocking, or hand spinning may also occur. Differentiating these symptoms from those of obsessive-compulsive disorder (OCD) can be challenging, so this study covers treatments for Autism Spectrum Disorders (ASDs). Treatments may address irritability, significant outbursts of rage and/or violence, and impulsivity towards oneself or others[35]. The most commonly used psychiatric medications for managing the behavioral symptoms associated with ASDs are discussed:

Serotonin Reuptake Inhibitors (SRI_S): Antipsychotics are the most effective medications for treating agitation in autism spectrum disorders and may also be beneficial for addressing other symptoms. However, they are less effective and better tolerated in children with autism compared to adults[34]. In contrast to individuals with ADHD, psychostimulants are less effective and have more adverse side effects when used to treat hyperactivity and inattention in individuals with ASDs[35].

8.2. Clomipramine: Clomipramine has been shown to be beneficial in treating hyperactivity, aggression, and repetitive behaviors in some individuals with autism spectrum disorder. However, it can have significant adverse effects on many individuals, especially adolescents and children, including increased irritability, self-mutilation, and sensitivity to loud noises[36]. Dosages ranging from 75 to 250 mg/day have been documented in several studies, with reported side effects ranging from mild to severe, such as insomnia, constipation, dry mouth, fatigue or lethargy, muscular dystonia, behavioral problems, and depression[34].

8.3. Fluvoxamine: While some individuals with autism find it beneficial for managing their behavior and anger, it has a minimal effect on adolescents and adults with autism[37]. According to specific studies, the adverse effects of doses in children ranged from 25 to 250 mg/day, whereas doses in adults varied between 50 and 300 mg/day. Adverse effects in children included anxiety, insomnia,

aggression, changes in appetite, difficulty concentrating, irritability, and increased impulsivity[36].

8.4. Fluoxetine: Studies have shown that fluoxetine is more effective in treating adolescents and adults with autism than in addressing repetitive behaviors in children. Adolescents appear to be more adversely affected compared to adults. According to various case reports involving adults, fluoxetine alleviates symptoms of obsessive-compulsive disorder, repetitive behaviors, and tantrums[38].

8.5. Sertraline: For individuals with ASDs, sertraline is considered to be reasonably well tolerated and effective in managing repetitive and aggressive behaviors. Studies suggest that adults can tolerate doses ranging from 25 to 200 mg/day, while children typically receive doses between 25 and 50 mg/day, with behavior worsening at around 75 mg/day. If sertraline is discontinued due to increased self-stimulation, heightened agitation or anxiety, or a fainting episode, it is important to consult with a healthcare provider[39].

8.6. Citalopram: Adolescents and children with ASDs who display repetitive behaviors may derive some benefit from Citalopram, although its effectiveness is constrained. Nevertheless, certain studies suggest that it could be beneficial in addressing various symptoms. Currently, there is no published research on the use of citalopram in adults with ASDs. Two retrospective evaluations involving adolescents and children observed positive responses to this medication. These responses encompassed a range of symptoms including aggressiveness, obsessions, repetitive behaviors, anxiety, and mood disorders[40].

8.7. Escitalopram: Preliminary research suggests that this medication may be less effective in treating adolescents and children with ASDs due to dose-related side effects. Currently, there is no published research on the use of escitalopram in adults with ASDs[41].

8.8. Venlafaxine: This selective serotonin as well as norepinephrine reuptake inhibitor has modest promise in treating ASDs in adolescents, children, and adults[42].

8.9. Mirtazapine: Research indicates that there is some efficacy in addressing certain symptoms linked to autism, such as improper sexual conduct. A 35% response rate was observed in terms of improvements in irritability, aggression, anxiety, hyperactivity, depression, and insomnia. Daily doses varied from 7.5 to 45 mg[43].

8.10. Haloperidol: It was demonstrated that haloperidol is beneficial in the long run for treating autism symptoms in adolescents and children and is more effective than clomipramine in treating irritability in adults[44]. Research on children has shown that haloperidol is more effective than a placebo in reducing stereotypes and social withdrawal in children older than four. Additionally, the medication has been shown to be successful in treating maladaptive behaviors in children for at least six months when they occur. The most significant response is seen in individuals experiencing anger and irritation, with research indicating that the typical daily dosage ranges from 0.5 to 4.0 mg[42].

8.11. Pimozide: Although there aren't many studies on its use in the treatment of autism disorders, it is one of the antibiotics that might help children with autism manage their sleep and sleep disorders. According to studies, the daily dose varies from 1 to 9 mg[44].

8.12. Clazopine: It is the first atypical antidote approved for use in US. Because it lowers the seizure threshold and increases the risk of agranulocytosis, its use in ASDs is restricted[45].

8.13. Risperidone: Several controlled studies have demonstrated the effectiveness of risperidone in treating irritability in individuals with ASD in adolescents and children. One multisite trial, which led to the Food and Drug Administration (FDA) approving risperidone for this purpose, indicated that in one study, doses ranged between 0.5 and 3.5 mg/day, with side effects including weight gain, increased appetite, drowsiness, fatigue, anxiety, dizziness, upper respiratory infections, salivation, and rhinitis. In adults, doses ranged between 1 and 10 mg/day, with occasionally divided doses; these side effects included transient mild sedation as well as increased weight and appetite[46].

8.14. Olanzapine: Olanzapine has some efficacy in adults and is thought to be somewhat helpful in children with ASDs syndrome. However, it has side effects that include weight gain, sedation and increased appetite. According to studies, the dosage rate is between 2.5 and 20 mg per day[47].

8.15. Quetiapine: Although its usage is frequently restricted due to side effects such as sedation, weight gain, and behavioral disturbance, it is useful in treating individuals with autism[48].

8.16. Ziprasidone: In people with autism, it is somewhat useful, despite the lack of controlled trials. Sedation was noted as a side effect in several studies, with a dosage range of 10-160 mg/day[49].

8.17. Aripiprazole: It is thought to be useful in reducing irritability in adolescents and children with autism. The drug's negative effects, which included aggression, excessive salivation, hyperactivity, weight gain, dyskinesia, and depression, caused the dose range of 2.5–15 mg/day to be discontinued [50].

8.18. Paliperidone: Treatment with paliperidone palmitale, one of the sustained-release intramuscular formulations, has been shown to be successful in treating adolescents, children, and adults with ASD[51].

8.19. Methylphenidate (MPH): Although its usage may be restricted owing to negative effects, it is a psychostimulant that is fairly effective in treating hyperactivity in children with autism[52]. According to studies, children's dosage rates ranged from 7.5 to 50 mg per day, whereas pre-schoolers had divided doses of 5 to 20 mg per day. Adult dosage rates, on the other hand, were 40 mg per day[50].

8.20. Atomoxeline: Even though side effects could occasionally prevent its usage, this selective norepinephrine reuptake inhibitor is authorized for the treatment of ADHD in adolescents and children[53]. Based on research, the adverse effects have been mainly mild to severe and included gastrointestinal symptoms, appetite loss, ringing in the ears, irritability, sleep issues, mood changes, and sedation. The average dose was found to range between 1.2 and 1.4 mg/kg/day. Yet, research revealed that side effects accounted for a high 42% of discontinuation rates[54].

8.21. Clonidine: For the mild treatment of hyperactivity and irritability in children with ASDs, use oral or transdermal clonidine[55]. According to published studies, the dosage rate varied between 0.1 and 0.2 mg per day, with sedation, drowsiness and reduced activity as adverse effects[56].

8.22. Guanfacine: Research indicates that the medication is generally well taken and that the dose varies from 0.25 to 9 mg/day[57]. However, common adverse effects include constipation, headaches, irritability, drowsiness, and nocturnal enuresis[58].

8.23. D-Cycloserine: D-cycloserine was administered at doses of 30, 50, and 85 mg/day for two weeks each, according to studies; the highest dose resulted in a 60% reduction in the severity of symptoms. Side effects included severe motor spasms in two different locations[58].

8.24. Memantine: While the US FDA has approved it as one of the Anti-NMDA receptor encephalitis antagonists for the treatment of Alzheimer's dementia, preliminary research has shown that it is also beneficial in treating social impairment as well as other symptoms in people with autism syndrome[56]. Memantin was administered at doses of 2.5–30 mg per day, and some studies reported adverse effects such as skin rash, irritability, increased hunger, vomiting, frequent seizures, and excessive drowsiness; however, no side effects were reported in another study [59] as shown in Table 2.

Table 2: Potential medical causes of behaviors associated with autism.

Speech Delay or Lack of Speech	Developmental Delay	Sleep Issues	Irritability and/or Aggression	Anxiety and/or OCD	Sensory Issues	Toe Walking
• Seizures • Sleep Apnea • Cerebral Folate Deficiency • Vitamin and/or Mineral Deficiencies: · Essential Fatty Acids (EFA) · Vitamin B12 · Vitamin B1 · Vitamin B6 · 5MTHF · Magnesium · Creatine · L-Carnitine · CoQ10 · Sulfur-Rich Compounds · Iron · Butyrate • Tongue-tie • Retained Primitive Reflexes • Mitochondrial Dysfunction	• Cerebral Folate Deficiency • Seizures • Vitamin and/or Mineral Deficiencies: · Vitamin B12 · Thiamine • Mitochondrial Dysfunction • Thyroid Disorders: · Hypothyroidism · Hyperthyroidism · Hashimoto's • Retained Primitive Reflexes: · Asymmetrical Tonic Neck Reflex • Immune Dysfunction • Toxic Mold Exposure	• Seizures • Gastrointestinal Issues: · Constipation · GERD (Reflux) · Gut Dysbiosis • Vitamin and/or Mineral Deficiencies: · Magnesium · Potassium · Vitamin D · Iron · Methyl Donors • Cerebral Folate Deficiency • Allergies • Enlarged Adenoids and Tonsils • Food Sensitivities • Low Blood Sugar • Problems with Sulfation • EMF Exposure • Excess Glutamate in the Brain • Mitochondrial Dysfunction	• Unrecognized Pain Caused By: · Gastrointestinal Issue · Headache/Migraine · Sinus Infection/ Congestion · Ear Infection · Dental Issue • Anxiety • Seizures • Vitamin and/or Mineral Deficiencies: · Lithium Orotate · Folate · Magnesium • Low Cholesterol • Chronic, Underlying Infection(s): · PANS/PANDAS · Lyme or Lyme Co-infections · Clostridia • Low Blood Sugar • Adrenal Fatigue and Low Cortisol • Lead or Other Heavy Metal Toxicity • Elevated Ammonia • Hormonal Imbalance • Food Allergies and/or Sensitivities	• PANS/PANDAS • Cerebral Folate Deficiency • Low Cholesterol • Vitamin and/or Mineral Deficiencies: · Iron · Zinc · Vitamin B1 · Vitamin B6 · Folate/Vitamin B9 · Vitamin B12 • Elevated Glutamate and Low GABA • Elevated Histamine • Gastrointestinal Issues: · Overgrowth of Pathogenic Bacteria in the Gut · Low Diversity in Gut Flora • Neuroinflammation • Poor Adrenal Function and Nor-epinephrine Regulation • Retained Primitive Reflexes	• Vitamin and/or Mineral Deficiencies: · Low B6 (p5p) · Magnesium • Food Intolerance(s) • Gastrointestinal Issues: · Fungal or Bacterial Overgrowth in the Gut • Problems with Sulfation • Underlying Infection(s): · Strep · Lyme • Excessive Amounts of Heavy Metals in the Blood or Tissues • Retained Primitive Reflexes	• Constipation • Vitamin and/or Mineral Deficiencies: · Magnesium · Zinc · Thiamine • Food Allergies and/or Sensitivities • Developmental Vision Problem • Retained Primitive Reflexes: · Tonic Labyrinthine Reflex

Stimming	Echolalia	Picky Eating	Pica	Hyperlexia	Hypotonia (Low Muscle Tone)	Inattention or Lack of Focus
• Gastrointestinal Issues: · Constipation · Gut Dysbiosis • Seizures • Food Allergies and/ or Sensitivities • Low Cholesterol • Mineral Deficiencies: · Zinc · Magnesium • Elevated Glutamate in the Brain • Retained Primitive Reflexes • Elevated Ammonia • Asterixis Due to Encephalopathy	• Seizures • Food Allergies and/ or Sensitivities • Gastrointestinal Pain: · Constipation • Mineral Deficiencies: · Zinc · Magnesium • Elevated Glutamate in the Brain • Elevated Ammonia • Low Cholesterol	• Gastrointestinal Issues: · Constipation · GERD (Reflux) · Eosinophilic Esophagitis · Gut Dysbiosis • Tooth Pain • Mineral Deficiencies: · Zinc • PANS/PANDAS • Food Allergies and/ or Sensitivities • Retained Primitive Reflexes	• Vitamin and/ or Mineral Deficiencies: · Iron · Zinc · Thiamine • Gut Dysbiosis • Parasitic Infection • Tooth Pain	• Brain Imbalance: · One Side of the Brain Stronger Than the Other	• Mitochondrial Dysfunction • Mineral Deficiencies: · Zinc · Magnesium	• Seizures • Food Sensitivities: · Dairy · Gluten · Dyes • Vitamin and/ or Mineral Deficiencies: · Iron · Magnesium · Vitamin D · Zinc · Folate • Reduced Blood Flow in the Brain • Gut Dysbiosis • Retained Primitive Reflexes: · Moro Reflex

Sources for all information contained in this chart can be found on our website: https://tacanow.org/family-resources/underlying-medical-issues-in-autism/

Please note: This chart does not contain an exhaustive list of medical issues that can cause behaviors associated with autism. It was created for informational purposes only and should not be used as a substitute for professional advice, diagnosis, or treatment. Always seek the advice of a qualified health care provider with any questions or concerns you may have.

2. Conclusion and future scope

Differences in behavior, communication, social interaction, specific interests, and sensory processing are characteristics of autism, a neurodevelopmental condition that affects individuals throughout their lives. These differences can make it challenging for those on the autism spectrum to interact effectively with their environment. In order for an individual to receive a diagnosis of autism, their symptoms must have been present since childhood and must interfere with their daily activities. This study has delved into autism in greater detail, offering a comprehensive review of its causes, manifestations, diagnosis, and prognosis. The rapid progress in identifying risk genes for Autism Spectrum Disorders (ASDs) is attributed to human genetic research. By categorizing individuals based on their genetic makeup—a process known as genotype-first—connections between genotype and phenotype are starting to emerge, despite the considerable genetic and clinical diversity that underlies ASDs. Understanding the molecular pathways associated with ASDs will be enhanced

through the integration of genetics with clinical symptoms and other functional genomic approaches such as epigenomics and transcriptomics.

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