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# A multidimensional review of autism spectrum disorder in Türkiye and the world

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## Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by persistent difficulties in social communication, restricted and repetitive behaviors, and atypical sensory processing, significantly affecting the quality of life of individuals, families, and society. Its etiology is complex and multifactorial, involving interactions among genetic, epigenetic, and environmental factors that influence brain development, synaptic function, and neural connectivity. This narrative review aims to provide a comprehensive and multidimensional overview of ASD by synthesizing current evidence on neuropathology, neuroimaging findings, molecular and cellular mechanisms, and major genetic and environmental risk factors. In addition, global and national epidemiological data were summarized, followed by an overview of current diagnostic criteria, screening strategies, and both pharmacological and non-pharmacological interventions, including behavioral, educational, and psychosocial approaches. Emerging research on novel therapeutic targets was also discussed. This review was conducted as a narrative review based on a literature search of major academic databases, international health reports, and current clinical guidelines. Relevant studies were selected to provide a comprehensive and integrative perspective on ASD. Finally, this review highlights the relevance of ASD in midwifery practice, emphasizing the role of midwives in prenatal risk assessment, perinatal care, early recognition, family support, and interdisciplinary collaboration. By integrating biological, clinical, and professional perspectives, this article aims to inform healthcare professionals and contribute to a more holistic, family-centered approach to ASD.

***Keywords:*** Autism spectrum disorder; Neurodevelopment; Neuropathology; Molecular mechanisms; Epidemiology; Midwifery

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## 1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent difficulties in social communication, restricted interests, and repetitive behaviors.[1-3] Symptoms typically emerge in early childhood, often before the age of three; however, many children do not receive a comprehensive evaluation at this stage, and

diagnosis may be delayed.[4,5] In recent years, the reported prevalence of ASD has increased considerably, with more than 1% of children in many Western countries being diagnosed with the disorder.[1,3]

The etiology of ASD is complex and multifactorial, involving interactions among genetic, epigenetic, and environmental factors that influence neurodevelopment. While genetic predisposition plays a central role, growing evidence suggests that environmental exposures and epigenetic mechanisms also contribute to the development and heterogeneity of the disorder.[1,3,6] Clinically, ASD presents with a wide spectrum of symptoms, and the severity and manifestation of social, communicative, and behavioral impairments vary significantly among individuals.

Early diagnosis and timely intervention are critical for improving developmental outcomes and quality of life in individuals with ASD. Accordingly, ongoing efforts focus on refining diagnostic criteria, improving the reliability of screening tools, and promoting comprehensive assessment processes.[3,5] Current management approaches are multidisciplinary and may include individualized behavioral and educational interventions alongside pharmacological treatments when appropriate.[1,6,7] Given its lifelong impact, ASD represents a significant challenge at both individual and societal levels, highlighting the need for continued interdisciplinary research to better understand its underlying mechanisms and develop more effective interventions.[8]

This narrative review aims to synthesize current knowledge on ASD from multiple complementary perspectives. It provides an overview of neuropathological and neuroimaging findings, key molecular and cellular mechanisms, and major genetic and environmental risk factors. In addition, global and national (Türkiye) epidemiological data are presented, followed by a summary of contemporary diagnostic criteria, screening approaches, and both pharmacological and non-pharmacological treatment strategies. Emerging research on promising therapeutic approaches is also discussed. Finally, this review highlights the relevance of ASD in midwifery practice. Midwives play a critical role in prenatal risk assessment, perinatal care, early recognition, family support, and interdisciplinary collaboration. By integrating biological, clinical, and professional perspectives, this review aims to contribute to a more comprehensive, evidence-based, and family-centered approach to ASD care.

## 2. Historical overview of autism spectrum disorder

The history of ASD dates back to the seminal observations of Leo Kanner in 1943, who first described autism as a condition characterized by marked differences in social communication and behavior.[9] This early definition laid the foundation for ongoing debates regarding the classification, subtypes, and diagnostic thresholds of autism.[10] Over time, substantial revisions have been made to the diagnostic criteria and conceptualization of ASD. Notably, the term "infantile autism," used in earlier diagnostic manuals such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III, has evolved into the broader and more inclusive category of "autism spectrum disorder" in DSM-5.[11]

These changes in classification reflect the complex and heterogeneous nature of ASD. Currently, diagnosis is primarily based on clinical observation, focusing on persistent deficits in social communication and the presence of restricted and repetitive patterns of behavior.[3,12] In parallel with evolving diagnostic frameworks and increased awareness, reported prevalence rates of ASD have risen significantly in recent decades.[3,4,10]

Although early research emphasized environmental explanations, contemporary evidence supports a multifactorial etiology involving genetic, epigenetic, and environmental factors. Genetic studies have identified numerous risk genes associated with neurodevelopment, synaptic function, and social behavior, while epigenetic mechanisms and environmental exposures further contribute to phenotypic variability.[13,14] Overall, the historical development of ASD reflects a transition from narrow diagnostic definitions to a multidimensional and spectrum-based understanding of the disorder.[3,11,12]

## 3. Neuroimaging findings in autism spectrum disorder

Neuroimaging studies have revealed that ASD is associated with widespread but heterogeneous alterations in brain structure and function. Importantly, no single or consistent neuroanatomical abnormality has been identified, highlighting the complexity of the disorder.

Structural imaging studies indicate that abnormalities may occur across multiple brain regions, including the cerebellum, cerebral cortex, thalamus, basal ganglia, and limbic system. Among these, cerebellar changes—particularly the loss of Purkinje cells—represent one of the most consistently reported findings in both postmortem and imaging studies.[15,16]

Large-scale magnetic resonance imaging (MRI) studies have demonstrated variability in cortical architecture

among individuals with ASD. Distinct neuroanatomical subtypes have been identified, including patterns of cortical thickening with increased surface area and cortical thinning with altered cortical organization. These subtypes are associated with differences in symptom severity and patterns of brain connectivity.[17,18]

Volumetric studies have reported changes in total brain volume and in specific regions, including the amygdala, corpus callosum, cerebellum, and caudate nucleus.[16] In addition, disruptions in white matter tracts suggest impairments in neural connectivity, which may underlie communication deficits observed in ASD.

Imaging studies, including functional and structural MRI studies, have further demonstrated altered connectivity within large-scale brain networks, particularly those involved in social cognition and executive functioning.[19-22] Both hypo-connectivity and hyper-connectivity patterns have been reported, depending on the developmental stage and functional context.[19,20]

Advanced imaging modalities, such as positron emission tomography and single photon emission computed tomography, have provided insights into neurochemical alterations in ASD, including imbalances in neurotransmitter systems, such as glutamate and gamma-aminobutyric acid (GABA).[19]

Despite these advances, a universally accepted neuroimaging biomarker for ASD has not yet been identified. The heterogeneity of findings, combined with the presence of comorbid conditions, continues to challenge interpretation and clinical application. Future large-scale, multimodal, and longitudinal imaging studies are expected to improve understanding of the neurobiological basis of ASD and support the development of individualized diagnostic and therapeutic strategies.[19]

## 4. Neuropathology of autism spectrum disorder

Autism spectrum disorder is associated with early and widespread alterations in brain development affecting multiple neural systems.[23,24]

### 4.1. Macroscopic and microscopic results

Studies have frequently reported increased brain volume and alterations in gray and white matter ratios in individuals with ASD. Although no single microscopic pathology is pathognomonic for ASD, several consistent findings have been described. These include cortical dysplasia, abnormalities in minicolumn organization (minicolumnopathy), and a reduction in cerebellar Purkinje cells.[24] While the overall laminar structure of the cerebral cortex is generally preserved, disruptions in cortical organization and myelination abnormalities are commonly observed.

### 4.2. Affected brain regions

Key brain regions implicated in ASD include the frontal cortex, cerebellum, amygdala, hippocampus, and brainstem. In particular, cerebellar abnormalities, such as Purkinje cell loss and structural dysplasia, are among the most robust findings. Alterations in the limbic system, including increased cell density and reduced neuronal size, have also been reported.[25] Additionally, neuronal migration abnormalities, heterotopic neuronal clusters, and multifocal dysplasias have been identified in both cortical and subcortical regions (Table 1).

### 4.3. Synaptic and molecular level results

Disruptions in synaptic organization and neurotransmitter systems (especially the GABAergic and glutamatergic systems) have been identified in patients with autism. Furthermore, alterations in glial cells and synaptic proteins (e.g., neurexin, SH3 and multiple ankyrin repeat domains [SHANK], and neuroligin) play an important role in the pathogenesis of autism.[23,26] At the molecular level, abnormal gene expression, epigenetic changes, and immune system-related pathways may play roles in autism.[23]

## 5. Embryological and developmental perspective

Abnormalities in brain development during prenatal and early postnatal periods have been strongly associated with ASD. Disruptions in key neurodevelopmental processes—including neurogenesis, neuronal migration, and the maturation of specific brain regions—support the view that ASD originates, at least in part, during early embryological development.[24,27] These alterations may affect the structural and functional organization of neural circuits, contributing to the characteristic features of the disorder. Importantly, disturbances in the timing and coordination of brain development are considered critical factors underlying the clinical heterogeneity of ASD.[28,29] Variability in when and how these disruptions occur may lead to differences in symptom severity, cognitive profiles, and behavioral manifestations across individuals. From a developmental perspective, ASD reflects a complex interplay of early neurobiological events rather than a single localized abnormality. Although neuropathological findings—such as minicolumn abnormalities, cortical and cerebellar dysplasias, and synaptic-level alterations—have been described in ASD, these should be interpreted within the broader context of disrupted developmental trajectories rather than isolated structural defects.[2,27,28] Overall,

**Table 1. Structural and functional brain findings in ASD and major sources of inter-study heterogeneity**

| Domain/Measure | Main findings reported in ASD | Sources of heterogeneity across studies | Implications for biomarker development |
|---|---|---|---|
| Total brain volume and head circumference | Early brain overgrowth in some children; differences often diminish or reverse over time | Age at assessment, developmental stage, sample size, and inclusion criteria | Effects are not consistent across all individuals and age groups; not specific |
| Cortical thickness and surface area | Regional increases or decreases in thickness; altered cortical folding and surface area | Region-of-interest selection, imaging methods, and age-related trajectories | Patterns vary between studies, limiting their use as a single diagnostic marker |
| White matter integrity (DTI measures) | Altered fractional anisotropy and diffusivity in major tracts (e.g., corpus callosum, long association fibres) | Differences in tractography methods, motion artefacts, and comorbidities (e.g., ADHD) | Abnormalities are common but non-specific and influenced by technical factors |
| Subcortical structures (amygdala, hippocampus, basal ganglia) | Volume and shape differences reported, sometimes enlarged, sometimes reduced, or unchanged | Small and heterogeneous samples, medication status, IQ, and sex differences | No consistent pattern across studies; findings are not robust enough as biomarkers |
| Cerebellum | Reports of altered vermis and hemispheric volumes, connectivity changes with cortical regions | Variability in segmentation protocols, age, and comorbid neurological conditions | Suggest involvement, but lack uniform direction or magnitude of change |
| Functional connectivity (resting-state networks) | Altered connectivity within and between major networks (e.g., default mode, salience, social brain networks) | Preprocessing pipelines, motion correction, task vs. resting-state differences | Network-level alterations are frequent but heterogeneous, limiting specificity |
| Task-related activation (fMRI) | Atypical activation patterns during social, language, and sensory tasks | Task design, performance differences, and developmental stage | Useful for understanding mechanisms, but too variable for a single biomarker |
| Overall conclusion | Multiple structural and functional differences are observed, but results are inconsistent and context-dependent | - | Current imaging findings do not support a single, uniform biomarker for ASD; a multimodal, dimensional approach is more appropriate |

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder; ASD: Autism spectrum disorder; DTI: Diffusion tensor imaging; fMRI: Functional magnetic resonance imaging.

current evidence suggests that ASD is a multidimensional neurodevelopmental condition with origins in early brain development, shaped by dynamic interactions between genetic, epigenetic, and environmental influences.

## 6. Molecular mechanism and signalling pathways of autism spectrum disorder

Autism spectrum disorder is a complex neurodevelopmental condition with a strong genetic component. In recent years, numerous genes have been associated with ASD, many of which are involved in essential molecular processes such as transcription, translation, synaptic transmission, epigenetic regulation, and immune–inflammatory responses. These molecular alterations converge on key signaling pathways that regulate brain development and function. Understanding these pathways is essential for elucidating ASD pathophysiology and identifying potential therapeutic targets.[29-31] Among these, the WNT signaling pathway plays a critical role in cell fate determination, neuronal migration, neural patterning, and organogenesis. Dysregulation of WNT signaling has been associated with impairments in synaptic function, oxidative stress responses, neurogenesis, and cellular metabolism. Experimental studies suggest that modulation of this pathway may alleviate ASD-like behaviors in animal models.[30]

The mechanistic target of rapamycin complex 1 (mTORC1) pathway is another key regulator implicated in ASD. Disruption of mTORC1 signaling has been identified as a shared molecular mechanism in both syndromic and non-syndromic forms of ASD. Alterations in this pathway can impair neuronal growth, synaptic plasticity, and protein synthesis, thereby contributing to abnormal neurodevelopment.[32]

Bone morphogenetic protein (BMP) and transforming growth factor-beta (TGF-β) signaling pathways are central to central nervous system development. These pathways regulate neural tube patterning, neural stem cell proliferation, differentiation, and synaptic organization.

Canonical SMAD-dependent signaling contributes to the balance between neurogenesis and gliogenesis, as well as overall brain structural organization.[31,32] TGF-β signaling additionally plays a role in neuronal survival, synaptic plasticity, immune regulation, and neurovascular interactions.[33] Alterations in TGF-β isoforms, particularly TGF-β1 and TGF-β2, have been reported in individuals with ASD, with associations to immune activation and symptom severity.[34,35] However, current evidence suggests that these alterations represent components of a broader dysregulated signaling network rather than specific diagnostic biomarkers.[29,36,37]

The sonic hedgehog (SHH) signaling pathway is a key morphogenetic system involved in dorsoventral patterning of the neural tube, neural progenitor proliferation, axonal guidance, and neuronal differentiation.[38,39] During embryogenesis, SHH gradients established by the notochord and floor plate regulate the formation of ventral neuronal subtypes and contribute to cortical and subcortical organization.[38] Beyond early development, SHH signaling continues to influence synaptic plasticity and neurogenesis. Dysregulation of this pathway has been implicated in ASD, with evidence suggesting altered SHH-related signaling, changes in circulating SHH levels, and interactions with oxidative stress pathways.[40,41]

Retinoic acid (RA) signaling contributes to neuronal differentiation, synaptic plasticity, and gene expression regulation. Although direct evidence linking RA signaling to ASD remains limited, it is considered a potential modulator of neurodevelopmental vulnerability through its interactions with other signaling pathways.

Fibroblast growth factor (FGF) signaling plays a crucial role in neurulation, regional patterning, and regulation of neural progenitor proliferation. In the developing cortex, FGF signaling influences neuronal identity, migration, and connectivity.[42–44] Intracellular FGFs also regulate ion channel activity and synaptic transmission, linking this pathway to neuronal excitability. Alterations in FGF signaling have been associated with atypical cortical development and early brain overgrowth in ASD; however, findings remain heterogeneous and insufficient for biomarker development.[43–46]

The phosphatase and tensin homolog (PTEN) pathway is particularly relevant in ASD subtypes associated with macrocephaly. Mutations in the *PTEN* gene disrupt downstream signaling cascades that affect neuronal growth, synaptic organization, and social behavior.[47] Lipid-based and redox signaling pathways, including prostaglandin E2 signaling and the endocannabinoid system, contribute to the regulation of neuroinflammation, oxidative stress, and synaptic plasticity in ASD.[48] Importantly, these pathways operate within an interconnected network. Crosstalk among pathways such as WNT, mTORC1, BMP, SHH, and TGF-β plays a crucial role in coordinating neurodevelopmental processes. Disruptions within this integrated signaling network are thought to underlie the biological complexity and clinical heterogeneity of ASD.[32,47,48]

In addition to intrinsic molecular mechanisms, external modulators such as gut microbiota, maternal immune activation, and environmental exposures may influence these pathways and contribute to ASD risk.[49] A comprehensive understanding of these mechanisms may facilitate the development of novel diagnostic biomarkers and targeted therapeutic strategies.

## 7. Etiology and risk factors of autism spectrum disorder

The etiology of ASD is multifactorial, involving the interaction of genetic, epigenetic, and environmental factors. There is no single causative mechanism, and different combinations of risk factors may contribute to the disorder in different individuals. ASD is considered a highly heritable condition. Twin and family studies demonstrate a strong genetic contribution, with heritability estimates indicating a substantial role of inherited susceptibility.[13,49–53] Hundreds of genes have been associated with ASD, particularly those involved in synaptic function, neuronal communication, and neurodevelopment.[54–56] Genetic variations include copy number variations, single-nucleotide polymorphisms, and rare mutations.[50–52] However, currently identified genetic alterations account for only a proportion of ASD cases, highlighting the contribution of additional mechanisms.

Epigenetic modifications, including DNA methylation and histone modifications, influence gene expression and may mediate the interaction between genetic susceptibility and environmental exposures.[50,51] Environmental risk factors include advanced parental age, prenatal infections, exposure to environmental toxins, and nutritional deficiencies during pregnancy.[49–52] The interaction between genetic and environmental factors is considered central to ASD development (Table 2).

Additional biological processes, such as immune system dysregulation and chronic inflammation, have been implicated in certain ASD subtypes.[53,54] Rare metabolic disorders, including abnormalities in amino acid transport and mitochondrial function, may also contribute to ASD in a limited number of cases.[55] Overall, ASD should be understood as a complex condition arising from the dynamic interplay of genetic, epigenetic, environmental, and biological factors rather than a single etiological pathway.

**Table 2. Primary factors and their contribution levels to autism spectrum disorder**

| Reason/Factor | Relative strength/ consistency of evidence | References |
|---|---|---|
| Genetic predisposition | High | 13,50,51,52,56 |
| Epigenetic changes | Medium | 13,14,53,57 |
| Environmental factors | Medium | 14,53,57,58 |
| Immune system dysfunction | Low-medium | 2,54 |
| Metabolic reasons | Low | 55 |

Note: The indications "high," "moderate, " and "low" refer to the relative strength and consistency of the evidence reported in epidemiological, genetic, and environmental studies cited in the text and are based on a narrative synthesis rather than precise quantitative effect sizes.

The development of ASD is governed by complex interactions between genetic, epigenetic, and environmental factors. There is no single cause, and different risk factors may be at the forefront for different individuals. Although research has made progress in understanding the causes of ASD[59-65], the exact causes remain unknown in many cases.

## 8. Epidemiology and burden of autism spectrum disorder

### 8.1. Global prevalence

Autism spectrum disorder is a globally prevalent neurodevelopmental condition, with current estimates suggesting that 1–2% of children are affected worldwide. Reported prevalence rates vary across regions, with higher estimates generally observed in high-income countries, largely due to differences in diagnostic practices, awareness, and access to healthcare services.[56,59,66,67] Epidemiological data indicate that ASD affects 10s of millions of individuals globally, representing a significant and growing public health concern. Earlier estimates suggested approximately 52 million cases worldwide, although more recent studies emphasize increasing recognition and diagnosis across diverse populations.[66] Prevalence rates vary considerably by region. In Europe, reported prevalence among children ranges from approximately 0.5% to over 3%, reflecting differences in screening and diagnostic methodologies.[68] In the United States, recent estimates indicate that approximately 1 in 36 children are diagnosed with ASD, corresponding to a prevalence of around 2–3%.[69] ASD is more frequently diagnosed in males than in females, with a male-to-female ratio ranging from 3:1 to 5:1. Age-specific differences have also been reported, with higher prevalence typically observed among school-aged children.[66]

### 8.2. Autism spectrum disorder in Türkiye

Interpretation of ASD prevalence in Türkiye requires caution due to limited nationwide epidemiological data. The available evidence is largely derived from regional studies, which may not fully represent the national population. Some regional studies suggest a prevalence of 87.8 per 10,000 children. However, this estimate should be interpreted carefully due to variations in study design, diagnostic criteria, and potential underdiagnosis.[70] Sociocultural factors also play a significant role in the perception and management of ASD in Türkiye. Media representations frequently emphasize terms such as "disability" and "treatment," which may contribute to stigma and reinforce societal misconceptions.[71] Studies conducted in Türkiye indicate that mothers of children with ASD often experience high levels of stress, depressive symptoms, and limited social support. Enhancing social support systems has been shown to improve maternal psychological well-being.[72] Although comprehensive national data are lacking, available evidence suggests that ASD diagnosis rates in Türkiye are increasing, likely reflecting improved awareness and expanding diagnostic practices.

### 8.3. Global burden and policy implications

Autism spectrum disorder represents a significant lifelong health burden with substantial clinical, economic, and social impacts. Individuals with ASD often require long-term multidisciplinary care, placing considerable strain on healthcare systems and families.[65] The burden of ASD is commonly assessed using measures such as disability-adjusted life years (DALYs). However, accurate DALY estimates must be derived from large-scale global epidemiological studies.[73] Given its increasing prevalence and long-term impact, ASD must be considered a priority in health policy planning. This includes the development of early screening programs, expansion of diagnostic services, and implementation of comprehensive support systems for affected individuals and families.[66] In Türkiye, additional challenges include social stigma, limited access to specialized services, and the psychosocial burden on families. Addressing these issues requires integrated healthcare and social policies, increased public awareness, and improved access to early intervention programs.

## 9. Midwifery and autism spectrum disorder

Rather than suggesting that midwifery alters the underlying neurodevelopmental mechanisms of ASD, this section focuses on the role of midwives as frontline professionals in prenatal, perinatal, and early postnatal care. Midwives play a key role in recognizing potential risk factors, supporting families, and facilitating timely

referral and interdisciplinary collaboration. Women with ASD may experience distinct challenges during pregnancy, childbirth, and the postpartum period. These challenges commonly include communication difficulties, heightened sensory sensitivity, and discomfort in clinical environments. Situations such as unfamiliar routines, physical examinations, and sensory overload during labor and postpartum care may negatively affect access to healthcare services and the overall care experience.[74,75] For this reason, midwifery care should adopt an individualized and patient-centered approach. Understanding the communication preferences and sensory needs of women with ASD is essential for providing safe and respectful care. Strategies such as clear and structured communication, minimizing sensory stimuli, and maintaining predictable care routines may improve patient satisfaction and clinical outcomes.[75–77]

In addition, mothers of children with ASD may experience increased psychological stress, depressive symptoms, and limited social support. Midwives and nurses play an important role in providing emotional support, guiding families, and facilitating early recognition and referral processes when developmental concerns arise.[76,77] Certain prenatal and obstetric factors—such as maternal infections, hypertension, bleeding, and medication exposure—have been reported in association with ASD. However, these relationships are complex and should not be interpreted as direct causation. Such factors may reflect underlying biological vulnerability or familial predisposition. Therefore, careful evaluation and evidence-based prenatal follow-up are essential. Overall, improving autism awareness in midwifery practice, strengthening communication strategies, and implementing individualized care models may contribute to more inclusive and effective maternal healthcare services.

## 10. Diagnosis and treatment of autism spectrum disorder

The diagnosis of ASD is primarily based on behavioral observations, developmental history, and standardized clinical assessment tools. Core diagnostic criteria include persistent deficits in social communication and interaction, together with restricted and repetitive patterns of behavior. Although symptoms typically emerge in early childhood, diagnosis may be delayed due to variability in clinical presentation and differences in access to specialized services. Recent research has increasingly focused on early detection, particularly in high-risk infants. Longitudinal developmental monitoring and detailed behavioral assessment approaches may support earlier identification of children who require further evaluation. In addition, potential biomarkers—such as neuroimaging findings, genetic indicators, and metabolic markers—are being investigated. However, these approaches are not yet sufficiently validated for routine clinical use and should be considered complementary to clinical assessment rather than diagnostic tools.[78]

Artificial intelligence and machine learning methods are also being explored as supportive tools in ASD research. These approaches may assist in analyzing complex datasets, including behavioral, neuroimaging, and genetic information. Nevertheless, their use in clinical diagnosis remains limited, and further validation is required before widespread implementation.[78,79] The primary goal of ASD management is to improve communication skills, adaptive functioning, and quality of life. Behavioral and educational interventions remain the cornerstone of treatment. Approaches such as early intensive behavioral intervention, developmental therapies, and parent-mediated programs have shown beneficial effects when tailored to individual needs.

Pharmacological treatments are mainly used to manage associated symptoms, including irritability, hyperactivity, anxiety, and sleep disturbances. However, there is currently no pharmacological intervention that directly targets the core features of ASD. Emerging approaches, including assistive communication technologies, digital interventions, and telehealth applications, may enhance access to care and support skill development. In addition, personalized approaches based on individual clinical and biological characteristics are being explored to address the heterogeneity of ASD.[78,79] In summary, the diagnosis and management of ASD require a multidisciplinary, individualized, and family-centered approach. Early recognition, structured assessment, and appropriate intervention planning are essential for improving long-term outcomes.

## 11. Research on autism and therapeutic agents

### 11.1. Preclinical models and experimental approaches

Research on ASD increasingly relies on preclinical models to understand underlying biological mechanisms and to identify potential therapeutic targets. Animal models, genetically engineered cellular systems, and stem cell–based approaches provide a strong scientific foundation for investigating the neurodevelopmental and molecular basis of ASD. Over the past three decades, rodent models—particularly mice and rats—have been the most widely used experimental systems. However, there has been a growing interest in alternative model organisms such as zebrafish,

*Drosophila*, and *Caenorhabditis elegans*, reflecting the need to better capture the biological heterogeneity of ASD.[80] These models enable the investigation of gene–environment interactions and allow for high-throughput screening of candidate therapeutic compounds. In addition, integrative studies combining human-induced pluripotent stem cell models with animal systems have provided important insights into ASD pathophysiology. Manipulation of high-risk genes such as *SHANK3*, *CNTNAP2*, *FMR1*, and *CHD8* has been shown to affect synaptic plasticity, neuronal differentiation, and behavioral phenotypes.[81] These findings support the role of these genes in neurodevelopmental processes relevant to ASD. Recent research has also focused on genetically engineered embryonic stem cell models carrying copy number variations associated with ASD. Studies using neuronal differentiation and single-cell RNA sequencing approaches have demonstrated cell-type-specific vulnerabilities, particularly in glutamatergic and GABAergic neurons, thereby strengthening evidence for the genetic and developmental mechanisms underlying ASD.[82,83] Overall, these experimental models are essential for advancing knowledge of ASD biology and for testing potential therapeutic strategies in preclinical settings.

### 11.2. Research fields and methodological approaches

Research on ASD encompasses both psychosocial and biological domains, each employing distinct methodological frameworks. In psychosocial research, intervention development typically follows a staged process. Initial efficacy studies are conducted under controlled conditions, followed by the development of structured intervention protocols and pilot testing. Subsequently, large-scale randomized controlled trials are performed in community settings to evaluate effectiveness and generalizability.[78,79,84]

In parallel with psychosocial research, biological and genetic studies have made significant progress in recent years. Advances in neurobiology, genetics, early diagnosis, and intervention strategies have expanded the understanding of ASD. Preclinical models, experimental therapeutics, biomarker research, and neurotechnological approaches are among the key areas of ongoing investigation.[47,80,84,85]

## 11.3. Therapeutic agents and treatment approaches

A wide range of therapeutic strategies has been investigated in ASD, although no single treatment addresses all aspects of the disorder. Emerging biological approaches include epigenetic enzyme inhibitors, which have shown potential in modulating gene expression and synaptic function in preclinical studies.[79] Pharmacological interventions are primarily used to manage associated symptoms rather than core features of ASD. Selective serotonin reuptake inhibitors have been explored for their potential role in synaptic development, although current findings remain inconsistent and require further investigation.[84] Similarly, atypical antipsychotics and antidepressants may be effective in reducing symptoms such as irritability or mood disturbances, but their impact on core social and communication deficits is limited.[85] Oxytocin has also been studied as a potential therapeutic agent due to its role in social behavior. However, findings remain inconclusive, and methodological limitations, including small sample sizes and heterogeneity in study design, have been highlighted in the literature.

Novel approaches, such as stem cell and secretome-based therapies, have gained increasing attention. Factors secreted by stem cells may exert immunomodulatory and neuroprotective effects, suggesting a potential role in alleviating ASD-related symptoms. Nevertheless, these approaches remain experimental and require further validation in clinical studies. Stem cell and secretome therapies, immune modulation factors secreted by stem cells, have been shown to have potential effects in alleviating autistic behavior (Table 3).[86,87]

## 12. Discussion

Defects in many cellular signaling pathways that regulate neuronal development, neurotransmission, metabolism, and immune responses have been identified in patients with ASD. The aim is to develop new biomarkers and treatment options by targeting these pathways.[85] New drug research, particularly focusing on epigenetic regulators, mTOR, WNT, and immune response pathways, is ongoing.[80] Currently, there is no effective pharmacological treatment for the core social symptoms of ASD. Research is progressing toward the development of safer and more effective drugs, the discovery of early-diagnosis biomarkers, and the dissemination of participatory and inclusive research models.[46,85,87]

Participatory research approaches and goals to improve the quality of life are at the forefront of next-generation therapeutic strategies.[86] Autism research is advancing rapidly in both the biological and psychosocial fields, and new therapeutic agents and targets are being developed. However, effective and safe treatments for the core symptoms remain limited. In the future, more inclusive and individualized approaches, early diagnosis, and innovative treatment methods are expected to be developed for this condition.

**Table 3. Research on autism spectrum disorder and the presentation of therapeutic agents**

| Therapeutic approach | Targeted areas | Research status and findings |
|---|---|---|
| Epigenetic enzyme inhibitors | Gene expression, synaptic function | Improvement in gene expression and behaviors observed in preclinical studies[80] |
| Selective serotonin reuptake inhibitors | Neurotransmission, synaptic development | Promising findings regarding early use, but further research is needed[84] |
| Atypical antipsychotics and antidepressants | Repetitive behaviors, irritability | Mixed results; while effective for some symptoms, limited effect on social core symptoms [85,87] |
| Oxytocin | Social interaction and behaviors | Inconsistent results; methodological and inclusivity issues highlighted in research[87] |
| Stem cell and secretome therapies | Neuroinflammation, immune modulation | The potential effect of factors secreted by stem cells in alleviating autistic behaviors has been shown[86] |

Autism spectrum disorder is a complex neurodevelopmental disorder that manifests as difficulties in social communication and repetitive behaviors and is caused by the interaction of genetic and environmental factors. Throughout history, its diagnostic criteria have evolved, and a significant increase in prevalence has been observed with increasing awareness of the disease. At the neuropathological level, early anomalies in brain development, minicholonopathy, cortical dysplasia, and synaptic disorders form the basis of ASD. At the molecular level, irregularities in mTOR, WNT/β-catenin, glutamatergic/GABAergic, calcium, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB), glycogen synthase kinase 3 (GSK3), and G protein-coupled receptor (GPCR) signaling pathways play an important role in pathogenesis. The causes of ASD include more than 250 genes, copy number variations, and prenatal environmental stress factors (such as air pollution and maternal infections). Although symptoms vary widely among individuals, the most common features are difficulties in social interaction, delayed language development, and repetitive behavior.

The prevalence of ASD is 0.7–1.0% worldwide and is more common in men. It has been reported that the prevalence is increasing in Türkiye, following a similar trend. Although the diagnosis is still based on behavioral observations, early phenotyping and biomarker identification are promising. Artificial intelligence and new-generation genetic analyses have the potential to improve diagnostic processes. In terms of treatment, behavioral and educational interventions are fundamental, whereas pharmacological approaches focus on managing accompanying symptoms. Artificial intelligence-assisted therapies and telehealth platforms have increased access to treatment. The quality of life for individuals with ASD has improved compared to the past, and pathways to greater independence have opened. Scientific research and public policies show promise for the future by supporting the full participation of individuals with ASD in society. Clinicians collaborating with families and community providers to provide accurate information, support, and hope will make a meaningful difference in patients' lives.

## 13. Conclusion

Autism spectrum disorder remains one of the most complex neurodevelopmental challenges of the 21st century, necessitating a multidimensional approach that spans from molecular biology to clinical practice. This review synthesizes current evidence indicating that the etiology of ASD is rooted in a sophisticated interplay between genetic predispositions, epigenetic modifications, and environmental triggers that disrupt early brain development and neural connectivity. The epidemiological data presented herein underscore a significant global increase in ASD prevalence, a trend also reflected in Turkey. In Türkiye, while awareness and diagnostic capabilities have improved substantially in recent years, there remains a pressing need for standardized national screening programs and longitudinal data to better map the prevalence and specific needs of the population.

Furthermore, the integration of advanced neuroimaging techniques and the emerging role of artificial intelligence in early diagnosis represent promising frontiers for improving long-term outcomes. This review also highlights the critical role of multidisciplinary care, emphasizing that healthcare professionals are in a unique position to facilitate early recognition and provide essential support to families during the perinatal period. Ultimately, addressing the challenges of ASD requires continued investment in research, development of targeted pharmacological interventions, and implementation of inclusive social policies. By bridging the gap between global scientific advancements and local clinical applications, it is possible

to enhance the quality of life of individuals with ASD and their families in Türkiye and worldwide.

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The authors declare they have no competing interests.

## Author contributions

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Not applicable.

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