Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD29688

Medical Interventions for Autism: Neurobiological Targets and Treatment Frontiers

Kaylee W. Zhao

Bentonville High School, Bentonville, USA
kayleezhao333@gmail.com

Abstract. Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent challenges in social interaction and behavior, and is frequently accompanied by comorbidities such as epilepsy, anxiety, and sleep disturbances. Conventional therapies including applied behavior analysis delivered via early intensive behavioral Intervention, speech-language therapy and symptom-focused pharmacological agents offer symptomatic relief, but require extensive resources and do not directly target underlying neurobiological mechanisms. Emerging interventions, including SHANK3 gene replacement and Excitation/Inhibition (E/I) modulators, remain in preclinical or early clinical stages but show strong potential to target core ASD symptoms at their biological source. Additionally, neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcranial ultrasound stimulation (TUS), may help reshape aberrant neural activity, with early evidence indicating improvements in language, cognition, and emotional regulation. Furthermore, biomarker-driven approaches using tools like EEG can support the development of personalized treatment plans tailored to individual neurobiological profiles. This review aims to evaluate the effectiveness of both conventional and novel treatment strategies and to propose an integrative framework that supports individualized, biologically informed care for individuals with ASD.

Keywords: autism spectrum disorder (ASD), neurobiological mechanisms, neuromodulation techniques, personalized treatment

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition marked by persistent challenges in social communication and interaction, along with restricted interests and repetitive behaviors. Individuals with ASD frequently present with comorbidities, including epilepsy, anxiety, and sleep disturbances, which make diagnosis and treatment more complicated [1]. According to surveillance data, about 1 in 31 children in the United States, around the age of 8, have been diagnosed with ASD, reflecting a 15% increase in just two years [2]. This rise is largely due to advances in diagnostic technologies and increased public awareness. Notably, autism is around 3.4 times more common in boys than in girls—a difference that may stem from both biological factors and long-standing underdiagnosis of girls, who often show less obvious symptoms [3]. Moreover,

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.LD29688

unequal access to healthcare across different regions and countries creates additional disparities in how autism is identified and managed.

Traditional treatment for ASD includes behavioral and educational interventions, such as ABA, speech therapy, and occupational therapy. These methods have been shown to significantly improve language, social engagement, and adaptive functioning, especially when introduced during early childhood [4]. They also offer highly personalized and flexible intervention plans, with content tailored based on the severity of symptoms and the unique learning profile of each child [5]. But at the same time, these approaches are time- and labor-intensive, often requiring consistent one-on-one sessions over extended periods [6]. Furthermore, behavioral and educational interventions do not address underlying neurobiological mechanisms, often resulting in transient behavioral gains. Additionally, pharmacological treatments, which include risperidone, aripiprazole, and similar medications, can help reduce associated behavioral problems such as aggression and hyperactivity, especially for children with severe comorbidities. These medications may also contribute to improved family stability and functioning [7]. However, many antipsychotics are associated with weight gain, drowsiness, hormonal imbalances, or extrapyramidal symptoms, particularly with long-term use.

Novel treatment strategies are gaining increasing attention. Gene and molecular-targeted therapies, such as mGluR5 modulators for Fragile X syndrome and mTOR inhibitors for tuberous sclerosis complex (TSC), aim to target the root genetic causes of autism in syndromic forms. These approaches are based on correcting genetic alterations and offer the potential for long-term neural modification rather than short-term symptom suppression, and have shown promise in reversing certain core biological abnormalities [8]. However, these treatments are still experimental, and most clinical trials remain at an early stage. Due to ethical and scientific challenges, their application is currently limited. Another novel treatment is non-invasive neuromodulation, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). This treatment can directly modulate abnormal brain activity in regions associated with social cognition, language, or repetitive behaviors. While early studies show encouraging results, safety protocols remain unstandardized and further large-scale validation is required. This review systematically examines multidimensional intervention strategies from the genetic level to neural networks, evaluates the clinical evidence and translational challenges in improving the core symptoms of autism, and explores future research directions, providing reference for the theoretical development and clinical application of more precise and personalized treatments.

2. Conventional treatment approaches

Applied behavior analysis (ABA) remains the most rigorously studied behavioral intervention for ASD, grounded in operant conditioning and learning theory, seeking to improve socially significant behaviors through systematically applied interventions. Its goal is to help individuals with autism acquire functional skills and reduce maladaptive behaviors by leveraging positive reinforcement, which strengthens desirable behaviors and may induce experience-dependent neuroplasticity—the brain's ability to reorganize itself through learning. ABA protocols are customized to each child’s cognitive profile, behavioral challenges, and developmental strengths. Two frequently used methods within ABA are Discrete Trial Training (DTT) and Natural Environment Training (NET). Through DTT, therapists break down complex skills into targeted, teachable units, reinforcing correct responses immediately and consistently. In contrast, NET integrates learning opportunities into naturally occurring activities like play or daily routines, promoting generalization of skills across real-life contexts [9]. The effectiveness of behavioral analysis (ABA) has been demonstrated,

DOI: 10.54254/2753-8818/2025.LD29688

especially in the early intensive behavioral intervention (EIBI). According to Eldevik et al., children receiving EIBI showed significant gains in cognitive and functional domains: an average increase of 11.98 points in full-scale IQ, 15.21 points in expressive language, and 5.92 points in adaptive behavior. However, ABA's strong focus on behavioral compliance may suppress natural autistic traits such as stimming, potentially undermining self-expression and emotional well-being. Intense, repetitive training protocols have been linked to increased stress, anxiety, and psychological distress, particularly in individuals who feel pressured to "mask" their autistic identity.

Speech-language therapy (SLT) is another foundational intervention, targeting deficits in verbal, nonverbal, and pragmatic communication. SLT plays a crucial role in developing expressive language, comprehension, and conversational turn-taking. Through structured practice and repetition, these therapies may help reinforce neural circuits responsible for language processing, social cognition, and sensorimotor integration. In a randomized controlled trial by [10], school-aged children with pragmatic language impairments—some with ASD—showed significant improvement in real-world communication and social engagement, even though structural language scores (e.g., grammar and syntax) remained unchanged. Despite its benefits, SLT can be resource-intensive, requiring consistent therapist involvement, caregiver participation, and access to specialized services, which may be limited by geographic or socioeconomic barriers.

Symptomatic pharmacotherapy aims to alleviate secondary symptoms associated with ASD, such as irritability, aggression, self-injurious behaviors, and severe anxiety. Second-generation antipsychotics, such as risperidone and aripiprazole, are commonly prescribed to reduce irritability, aggression, and self-injurious behaviors. In a randomized controlled trial [11], found that risperidone reduced irritability in children with autism by 56.9%, compared to a 14.1% reduction with placebo. These medications act primarily by modulating dopaminergic and serotonergic neurotransmission—specifically through antagonism or partial agonism at D2 and 5-HT2A receptors—thus stabilizing emotional regulation and effectively decreasing hyperactivity. Additionally, sedatives and anxiolytics, such as benzodiazepines or melatonin, are used to manage comorbid symptoms like anxiety and sleep disturbances. In a randomized crossover trial [12], found that melatonin significantly improved sleep onset and reduced nighttime awakenings in children with ASD, supporting its short-term safety and effectiveness. Benzodiazepines enhance GABAergic activity by binding to GABA-A receptors, leading to reduced neural excitability and calming effects. While these agents can improve sleep onset latency and reduce nighttime awakenings, they do not address core ASD symptoms, and long-term use carries risks of tolerance, dependence, and potential cognitive dulling

3. Novel treatment strategies

Recent advances in molecular neuroscience have spurred the development of gene and protein-targeted therapies aimed at correcting the root causes of syndromic forms of ASD. Among these, SHANK3 gene replacement using adeno-associated virus (AAV) vectors has shown great promise, particularly for individuals with SHANK3 mutations. SHANK3 encodes a synaptic scaffolding protein critical for maintaining the postsynaptic density by organizing and anchoring neurotransmitter receptors such as glutamate receptors. This protein is essential for proper synaptic formation, plasticity, and neural connectivity. Mutations in SHANK3 disrupt synaptic architecture, impairing neural communication and contributing to ASD-related behavioral deficits. In a pivotal study [12], demonstrated that AAV-mediated SHANK3 delivery in adult SHANK3-deficient mice restored synaptic function in the striatum and reversed key autism-like behaviors, including impaired social interaction and excessive grooming. Jaguar Gene Therapy's JAG201 exemplifies the

DOI: 10.54254/2753-8818/2025.LD29688

clinical translation of this strategy, employing an AAV9 vector to deliver a SHANK3 minigene directly to neurons in the central nervous system, with the potential to address core ASD symptoms at their biological source and improve quality of life. Excitation/Inhibition (E/I) balance modulation is a promising therapeutic approach targeting the disrupted equilibrium between excitatory glutamatergic and inhibitory GABAergic signaling commonly observed in ASD. In typical neurons, GABA receptors mediate inhibitory neurotransmission by allowing chloride ions (Cl^-) to enter the cell, hyperpolarizing the membrane and reducing excitability. In ASD, this inhibition is compromised due to altered chloride transporter function—specifically, increased activity of NKCC1 and reduced function of KCC2—which elevates intracellular chloride levels and causes GABAergic signaling to become paradoxically excitatory. This disrupts cortical circuitry and contributes to sensory and social dysfunction.

One pharmacological strategy uses bumetanide, a diuretic that inhibits NKCC1, thereby lowering intracellular chloride concentration and restoring GABA's inhibitory effect. A randomized controlled trial by [13]. Found that children with ASD treated with bumetanide for three months showed significant improvements in social responsiveness and sensory processing. These behavioral improvements were associated with reductions in GABA/Glx ratios in the insular cortex, measured via magnetic resonance spectroscopy (MRS), providing a neurochemical correlate of treatment efficacy. However, common side effects such as mild hypokalemia and increased urination were observed. An emerging alternative involves KCC2 activators, which promote chloride extrusion and enhance GABAergic inhibition without the systemic diuretic effects of bumetanide. Preclinical studies in rodents suggest these compounds can normalize cortical oscillations and improve social behavior, although further research is needed to optimize dosing and assess long-term safety in humans.

Non-invasive neuromodulation techniques offer a means to directly reshape aberrant neural network activity. Repetitive Transcranial Magnetic Stimulation (rTMS) delivers magnetic pulses to induce electric currents in targeted brain regions, such as the prefrontal-temporal network, modulating neuronal excitability and connectivity. This intervention can enhance social attention and reduce anxiety by normalizing dysfunctional cortical circuits. Transcranial Direct Current Stimulation (tDCS) applies low-intensity direct current (0.5–2 mA) to the scalp, subtly shifting neuronal membrane potentials. Anodal tDCS over language or executive control areas enhances long-term potentiation–like plasticity, boosting gains from concurrent speech or cognitive training, whereas cathodal stimulation can suppress hyperactive circuits. tDCS is well tolerated, with mild scalp tingling as the most common side effect, and may potentiate behavioral therapies' effects. Lastly, Transcranial Ultrasound Stimulation (TUS) uses low-intensity focused ultrasound waves (200–600 kHz) to precisely target deep brain structures such as the hippocampus and striatum, modulating neuronal activity with high spatial resolution. Depending on stimulation parameters—frequency, intensity, and pulse duration—TUS can excite or inhibit neural circuits involved in cognition and emotion regulation. While promising, TUS's safety, optimal dosing, and timing protocols require further investigation.

4. Challenges and future directions

4.1. Heterogeneity and precision stratification

ASD is not a uniform condition but a spectrum of endophenotypes, each characterized by distinct genetic, neurobiological, and behavioral features. This intrinsic heterogeneity poses a fundamental challenge to one-size-fits-all interventions, which underscores the need for personalized, stratified

DOI: 10.54254/2753-8818/2025.LD29688

intervention strategies tailored to each individual's unique profile. To this end, machine learning models that integrate multimodal data—including neuroimaging, genomic profiles, and behavioral metrics—can enable precise subtyping and prognosis prediction, advancing truly individualized care. Such stratification will inform tailored treatment regimens, enabling clinicians to match gene- or circuit-targeted therapies with the individuals most likely to benefit, and to adjust protocols dynamically as patients develop.

4.2. Scalability and access to care

Despite technological advances, scalability and resource disparities remain significant global barriers. Uneven healthcare infrastructure across rural and urban regions, as well as between developed and developing countries, limits access to timely diagnosis and effective intervention. The expansion of telehealth systems and home-based neuromodulation platforms offers a scalable solution, enabling remote, supervised therapies and reducing dependence on centralized clinical settings. However, successful implementation requires parallel investments in provider training, public awareness campaigns to reduce stigma, and rigorous quality-assurance frameworks to guard against misdiagnosis and suboptimal treatment.

4.3. Technological innovations and validation

Closed-loop neuromodulation systems, which adjust stimulation parameters in real time based on biomarkers such as EEG signals or behavioral feedback, represent a major advancement in adaptive, precision-guided therapy. In parallel, next-generation viral vectors and CRISPR-based gene editing technologies enable targeted modification of ASD-related genes, potentially offering durable molecular correction. Yet, these cutting-edge modalities demand comprehensive preclinical studies to elucidate off-target effects and immunogenicity, followed by carefully phased clinical trials with long-term follow-up to establish safety, durability of response, and optimal dosing regimens.

4.4. Ethical and societal framework

Future research and development must be grounded in a robust societal and ethical framework. Treatments should prioritize enhancing autonomy, communication, and quality of life, rather than enforcing neurotypical conformity. Incorporating neurodiversity perspectives into therapeutic design ensures that interventions uphold individual identities rather than suppress them. Moreover, stakeholders must evaluate long-term societal implications, including questions of access, insurance coverage, and the risk of exacerbating health inequities, to chart a path toward inclusive, ethically grounded translation of novel ASD treatments

5. Conclusion

In summary, this review explores the current and emerging treatment strategies for individuals with ASD, with a long-term goal of advancing person-centered, integrative care and social inclusion. Behavioral and educational interventions remain the foundation of ASD management, particularly when implemented early in development. These approaches have demonstrated effectiveness in improving social interaction, communication, and behavior regulation. While they may not directly target the neurobiological roots of ASD, prolonged and intensive application can enhance neuroplasticity, supporting greater functional independence over time. However, the high demands for time, staffing, and individualized implementation continue to limit accessibility, particularly in

DOI: 10.54254/2753-8818/2025.LD29688

under-resourced settings. Symptomatic pharmacological treatments also play a complementary role in managing co-occurring symptoms such as irritability, aggression, hyperactivity, and sleep disturbances. Though they do not target the core deficits of ASD, these medications can improve quality of life when used judiciously. With the rise of novel technologies, the integration of AI-driven tools, robotics, and digital platforms shows promise in enhancing the scalability, personalization, and efficiency of behavioral interventions.

Recent advances in molecular neuroscience have opened possibilities for root-level interventions, including SHANK3 gene replacement using adeno-associated virus (AAV) vectors. This targeted gene therapy aims to correct underlying synaptic abnormalities in specific syndromic forms of ASD. Similarly, modulation of excitation/inhibition (E/I) balance, via bumetanide or KCC2 activators, offers a pharmacological path to restore disrupted glutamatergic and GABAergic signaling, mitigating sensory and social impairments. Meanwhile, non-invasive neuromodulation techniques, such as rTMS, tDCS, and TUS, are emerging as potential tools for circuit-level repair. Although still under clinical investigation, these modalities may complement behavioral training to reshape dysfunctional neural circuits.

Given the clinical complexity and heterogeneity of ASD, future treatments should embrace an integrated biomarker-driven approach that unites behavioral, molecular, and neuromodulatory strategies. Objective biological indicators, such as genetic variants (e.g., SHANK3, CHD8), neurotransmitter imbalances, EEG oscillation patterns, and neuroimaging markers, can guide the personalization, selection, and dynamic adaptation of treatments. Stratifying individuals by these biomarkers enhances therapeutic precision and helps identify which patients are most likely to benefit from specific approaches like gene therapy or neuromodulation. Integrating behavioral outcomes with neurobiological feedback further allows for responsive, real-time treatment monitoring and refinement.

Robust clinical translation and regulatory approval require large-scale, randomized Phase II and III trials to validate the safety and efficacy of these novel interventions. Standardized safety protocols and consistent trial designs are crucial to ensuring reproducibility across settings. In addition, long-term monitoring is needed to assess durability of effects, adverse events, and ethical concerns related to autonomy and identity in patients undergoing biologically based interventions. Ultimately, the fusion of multidisciplinary strategies with technological innovation offers a transformative path forward. However, achieving truly equitable and sustainable progress requires attention to global healthcare disparities, increased public education, and ethical safeguards. Broadening access, enhancing affordability, and maintaining a person-centered focus will be critical in ensuring that all individuals with ASD, regardless of geographic or socioeconomic background, can benefit from the next generation of precision therapies. Acknowledgements If any, should be placed before the references section without numbering.

References

[1] Masi, A., DeMayo, M. M., Glozier, N. and Guastella, A. J. (2017) An overview of autism spectrum disorder, heterogeneity and treatment options. Neuroscience Bulletin, 33(2), 183–193.

[2] Maenner, M. J., Shaw, K. A., Bakian, A. V., Bilder, D. A., Durkin, M. S., Esler, A., et al. (2023) Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network. MMWR Surveillance Summaries, 72(2), 1–14.

[3] Loomes, R., Hull, L. and Mandy, W. P. L. (2017) What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry, 56(6), 466–474.

DOI: 10.54254/2753-8818/2025.LD29688

[4] Eikeseth, S. (2009) Outcome of comprehensive psycho-educational interventions for young children with autism. Research in Developmental Disabilities, 30(1), 158–178.
[5] Lord, C., Elsabbagh, M., Baird, G. and Veenstra-Vanderweele, J. (2018) Autism spectrum disorder. The Lancet, 392(10146), 508–520.
[6] Howard, J. S., Sparkman, C. R., Cohen, H. G., Green, G. and Stanislaw, H. (2005) A comparison of intensive behavior analytic and eclectic treatments for young children with autism. Research in Developmental Disabilities, 26(4), 359–383.
[7] Choueiri, R. and Zimmerman, A. W. (2017) Clinical features of autism spectrum disorder. In A. W. Zimmerman (Ed.), Autism: Current theories and evidence (pp. 49–72). New York: Humana Press.
[8] Thompson, B. L., Stanwood, G. D., Levitt, P. and Wallace, G. L. (2023) Translational strategies for developing circuit-based treatments for autism spectrum disorder. Nat. Neurosci., 26, 123–134.
[9] Granpeesheh, D., Tarbox, J. and Dixon, D. R. (2009) Applied behavior analytic interventions for children with autism: A description and review of treatment research. Behav. Anal. Today, 10(1), 7–19.
[10] Adams, C., Lockton, E., Freed, J., Gaile, J., Bowler, D. and Harvey, M. (2012) The Social Communication Intervention Project: A randomized controlled trial. Int J. Lang Commun. Disord., 47(3), 233–244.
[11] McCracken, J. T., McGough, J., Shah, B., Cronin, P., Hong, D. and Aman, M. G., et al., (2002) Risperidone in children with autism and serious behavioral problems. N Engl J. Med., 347(5), 314–321.
[12] Malow, B. A., Adkins, K. W., McGrew, S. G., Wang, L., Goldman, S. E., Fawkes, D. and Burnette, C. (2012) Melatonin for sleep in children with autism: A controlled trial. J Autism Dev. Disord., 42, 1729–1737.
[13] Lemonnier, E., Villeneuve, N., Sonie, S., Serret, S., Rosier, A., Roue, M. and Ben-Ari, Y. A. (2017) randomized controlled trial of bumetanide in the treatment of autism in children. Transl. Psychiatry, 7(3), e1056.