

Perspectives on Current and Emerging Treatments for Autism: Developing a Framework for Personalized Treatment Approaches

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ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with core symptoms of restricted, repetitive behaviors and social interaction deficits, often negatively impacting quality of life. Several treatments exist for ASD, though in many cases they do not completely address core symptoms. This paper holistically investigates behavioral, pharmacological, and gene therapy approaches to provide a framework to consider personalized treatment options. First, this article presents frequently utilized behavioral treatments, such as applied behavioral analysis and music therapy. Next, a summary of important pharmacological treatments is provided, such as risperidone and leucovorin. The article analyzes latest developments in gene therapy, which could be an excellent choice in the future for autistic individuals with identified monogenic causes. In each area, an analysis of the opportunities and limitations of these treatments is provided, along with scrutiny of applicable clinical trial results. This review explains how each treatment area involves tailoring of the options available to suit the needs of the patient in question, as well as combining these areas to help create further individual-specific approaches. Ethical considerations, such as those present in utilization of applied behavioral analysis, are also discussed as part of the development of treatment strategies. The deeper understanding provided here for each of these approaches is expected to help patients and caregivers in their process of selecting treatments. Continuing advances in ASD research, including combining treatment options, is needed to provide better outcomes for this global public health issue affecting tens of millions of individuals worldwide.

INTRODUCTION

Autism spectrum disorder (ASD, see glossary for a full description of all abbreviations used), commonly known as autism, is a highly heterogeneous neurodevelopmental disorder (Lord et al. 2022). ASD is prevalent worldwide, occurring in roughly 1-3% of the global population (Lim et al. 2018). Since the initial description of the condition by Leo Kanner in 1943, the prevalence of ASD has increased dramatically (Ratajczak 2011). There is significant evidence for a genetic component in the cause of ASD, with variants of numerous genes contributing to ASD symptoms and there being a significant likelihood of an individual having ASD if their monozygotic twin also has the condition (Ratajczak 2011). However, known combinations of genes and genetic disease associated with ASD account for only a

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small fraction of ASD cases, suggesting a much more complicated genetic cause comprised of numerous relatively rare mutations (Ratajczak 2011). Additionally, other factors which have been variously hypothesized to cause ASD include the toxicity of mercury, and imbalances in metal ratios in the body, though the true role of many of these factors in causing ASD is disputed (Ratajczak 2011).

The Diagnostic and Statistical Manual of Mental Disorders describes two broad symptoms of ASD: challenges in social interaction and communication as well as restricted, repetitive patterns of behaviors, interests, and activities (Lim et al. 2018). For example, individuals with ASD may struggle to communicate verbally, often struggling to start conversations, greet others, make requests, and understand non-verbal cues (Peterson et al. 2024). Such symptoms may be related to symptoms of sensitivity to loud noises and other sounds, which is also common among those with ASD (Peterson et al. 2024). Additionally, though disruptive behavior is not a core symptom of ASD, behaviors such as hyperactivity, inattention, aggression, and irritability are common for many (Anixt et al. 2024). The heterogeneity in the symptoms of ASD is often caused by the comorbidity of other psychiatric and neurologic conditions with ASD. Examples include attention and hyperactivity disorders, anxiety and depression (Lord et al. 2022), contributing to the variety of medical trajectories taken by those with ASD (Doshi-Velez et al. 2014). ASD is commonly diagnosed at an early age, following observations of a child's social interactions with adults and other individuals (Lord et al. 2022). General characteristics such as social reciprocity, communication, and repetitive behaviors are often assessed in the process of diagnosis (Lord et al. 2006).

The attention of scientists and clinicians to individuals with autism, including the study of the behaviors, strengths, and challenges of the conditions, can be dated back to over 500 years ago (Lord et al. 2022). The Lovaas Method of Applied Behavior Analysis, published in a 1987 article by Ole Ivar Lovaas, set the trajectory for intensive behavioral treatments for ASD (Aishworiya et al. 2022). Despite early diagnosis and intensive therapy, individuals with ASD often are challenged in their overall life experience, including in areas such as social and verbal interaction as well as academics (Peterson et al. 2024). For many with ASD, efficacious treatments can result in improved independence and quality of life in the long-term (Lord et al. 2022). A secondary motivating factor for ASD treatments may be cost, with the total annual cost of autism in the United States being about \$35 billion per year, with a lifetime per-capita societal cost of \$3.2 million. These costs largely represent losses in productivity and adult care (Dawson et al. 2009). Further research is necessary to determine the long-term needs of patients with ASD as well as the mechanisms behind treatments for ASD (Lord et al. 2022). Even then, support for treatments among those with ASD is not unanimous, with movements like the neurodiversity movement rejecting the notion of a "cure" for ASD and instead emphasizing the need for environments to adapt to support people with ASD (Lord et al. 2022). Overall, behavioral, rather than pharmacological, treatments have remained the primary form of treatment for the condition, attributed to the heterogeneous nature of ASD (Aishworiya et al. 2022).

The purpose of this review is to examine the role and effectiveness of various treatments for ASD, including the progression of such treatments from the relatively recent past to newly emerging and developing treatments, as well as the different purposes of various behavioral, pharmacological, and other treatments. As part of this, research studies and clinical trial results have been scrutinized. This analysis is

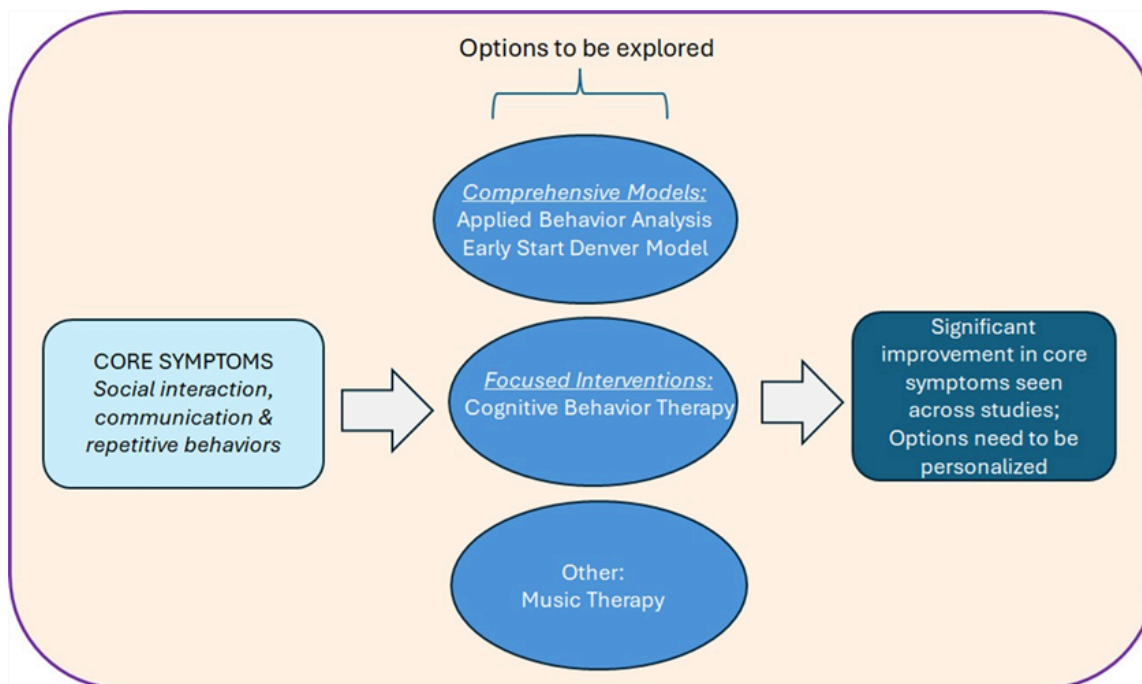
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expected to provide a deeper understanding of each treatment option which will benefit patients and caregivers as they consider their choices. This understanding, coupled with combination approaches as well as future gene therapy treatments, is expected to aid in the development of personalized options for patients suffering from ASD.

BEHAVIORAL TREATMENTS: THE MAINSTAY OF AUTISM TREATMENTS

Non-pharmacological treatments, particularly behavioral and psychological interventions, are currently the mainstay treatment for ASD (Aishworiya et al. 2022, Wood et al. 2019). For instance, more than half of children with ASD have been found to be treated with behavioral treatment (Xu et al. 2018). Seeing as ASD can be diagnosed at an early age, identifying the disorder in a child as early as possible may provide for more effective early interventions (Anixt et al. 2024). At this stage, where the brain is still developing, interventions are likely to shape the long-term development of ASD symptoms and are more likely to be effective (Anixt et al. 2024) For infants and toddlers in particular, participation in early intervention services is correlated with improvements in language, cognition, academics, and behavior (Anixt et al. 2024). In general, non-pharmacological, evidence-based interventions for ASD can be grouped into two categories: comprehensive treatment models, and evidence-based practices, also known as focused interventions (Anixt et al. 2024). The former uses broad learning and skill development to impact the core symptoms of ASD, including communication, social, and adaptive skills, while the latter teach individual skills or address a specific goal, serving as building blocks which can be combined to form educational programs for children with ASD (Anixt et al. 2024, Aishworiya et al. 2022). These categories of behavioral treatments and their use in addressing core symptoms of ASD are summarized in **Figure 1**.



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Figure 1. Summary of major behavioral treatments used to treat core symptoms of Autism Spectrum Disorders

Applied Behavioral Analysis: a personalized behavioral approach

Comprehensive treatment models commonly use applied behavior analysis (ABA) as an approach to achieve the goals of the intervention. ABA is a one-on-one, individualized therapeutic approach which attempts to enhance the skills of individuals with ASD in the contexts of their homes, schools, and communities (Peterson et al. 2024). ABA attempts to focus on solving socially meaningful problems in socially important settings, as opposed to experimentally analyzing behavior (Anixt et al. 2024, Slocum et al. 2014). ABA aims to promote growth in skill development in areas such as adaptive skills, functional communication, and emotional regulation and let these skills be generalized across a variety of environments (Anixt et al. 2024). Other forms of behavioral treatments include naturalistic developmental behavioral interactions (NDBI), which emphasizes engagement between the child and the intervention provider such that factors and consequences of a natural environment are simulated, as well as parent-mediated intervention, in which parents receive training to implement strategies in children to address core ASD symptoms (Anixt et al. 2024).

Behavioral treatments for ASD using ABA are reported to have generally seen improvements in ASD symptoms. Case in point is a study by Peterson et al. (2024) which administered at least 25 hours per week of ABA therapy to thirty-three individuals with autism and analyzed the impacts of the therapy on the verbal symptoms of ASD, including speaking and communication abilities (Peterson et al. 2024). The study used the Verbal Behavior Milestones Assessment and Placement Program (VBMAPP) and the Assessment of Basic Language and Learning Skills (ABLLS) to gauge improvements in mixed model ABA interventions (including discrete trial training, mass trials, and a naturalistic environment) on these verbal skills. The study found statistically significant improvements in various VBMAPP scales, such as manding skills (expression of wants and needs), tacting skills (naming entities), response to verbal stimuli, and a variety of social interactions (Peterson et al. 2024). Statistically significant improvements were found in all ABLLS scales, such as in using language to express needs, wants, and preferences; an increase in the ability to respond to verbal stimuli directly without physical cues (including generating novel responses to questions without prompting or restating); an increase in the ability to construct grammatically accurate sentences; as well as an increase in the ability to interact in socially appropriate ways (Peterson et al. 2024).

Additional improvements by integrating ABA with the Early Start Denver model

Additionally, comprehensive treatment program models like the Early Start Denver Model (ESDM), which integrates ABA with developmental and relationship-based approaches have also seen success (Anixt et al. 2024, Dawson et al. 2009). ESDM is specifically developed as an early intervention for infants to preschool aged children, including toddlers as young as 12 months, and is provided in the

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toddler's natural home environment (Dawson et al. 2009). A study by Dawson et al. (2009) randomly assigned 48 children between 18 and 30 months of age, all of whom met criteria for ASD by various diagnostic measures, into two groups: (1) an ESDM group which received 20 hours per week of ESDM intervention (in addition to other community interventions) and (2) an assess-and-monitor (A/M) group which received commonly available community providers for interventions, with each group being assessed yearly (Dawson et al. 2009). After two years of intervention, children in the ESDM group showed significant improvements in IQ, adaptive behavior, and diagnostic status compared to the A/M group; for example, while only 56% of children in the ESDM group retained their diagnosis for ASD, 71% of children retained their diagnosis in the A/M group (Dawson et al. 2009). Additionally, improvement in communicative abilities was also found in the ESDM group. While children in the A/M group fell farther behind in adaptive behavior, children in the ESDM group, though still delayed in this measure, remained steadier in development (Dawson et al. 2009). With this said, repetitive-behavior scores and Autism Diagnostic Observation Schedule (ADOS) scores did not change in either group, though improvements in other behaviors (including parental report) contributed to changes in diagnostic status. During the two-year period, no serious adverse effects related to the intervention were reported (Dawson et al. 2009).

Focused Interventions such as Cognitive Behavior Therapy

Several other treatment options specifically exist for the various symptoms of ASD. For example, evidence-based strategies specifically targeting communication skills include functional communication training, language training (production), and augmentative and alternative communication, which include various non-verbal communication systems (Anixt et al. 2024). Additionally, treatments for various co-occurring disruptive mental health conditions include parent training, cognitive behavioral therapy (CBT), and Facing Your Fears (Anixt et al. 2024). CBT, for instance, promotes evaluation of thoughts and behavior among patients with anxiety, and has been adapted for the specific purposes of treating individuals with ASD (Anixt et al. 2024, Wood et al. 2019). A study by Wood et al. (2019) randomly assigned patients with ASD (and maladaptive and interfering anxiety) into three groups: one with standard-of-practice CBT, one with CBT specifically adapted for ASD, and one with treatment as usual (Wood et al. 2019). The study found that both versions of CBT resulted in improvements, with the adaptive CBT program outperforming the other two programs in Pediatric Anxiety Rating Scores (Wood et al. 2019). On the Clinical Global Impressions-Improvement scale, both CBT treatments received rates of positive response higher than 80%, while treatment as usual only received a rate of 11% (Wood et al. 2019). Parent reports of social communication, adaptive functioning, and emotional dysregulation symptoms were also more favorable for the adapted CBT group. It is hypothesized that the modular nature of the adapted CBT, its specific tailoring to ASD symptoms such as social communication, and longer treatment sessions lead to the most favorable effects (Wood et al. 2019).

The promise of Music Therapy

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A treatment shown to have promising results in ASD treatment is music therapy (MT), showing improvements in regard to symptoms of social interaction and communication skills (Alayidh et al. 2025). MT utilizes musical experiences given to patients by therapists in both active forms and receptive forms. Active forms of MT include producing music through improvisation, songwriting, and singing, while receptive forms include listening to recorded or live music (Gassner et al. 2021). Alayidh et al. (2025) investigated nine randomized control trials and found measurable improvement in these aspects in all trials, with four studies reporting significant improvements in social communication skills and two others finding improved performance in verbal production and emotional responsiveness (Alayidh et al. 2025). Another review by Gassner et al. found improvements in behavior, social communication, brain connectivity, and parent-child relationship in patients with ASD from MT (Gassner et al. 2021). Efforts like these suggest that further research with larger sample sizes and extended study durations will likely further validate the beneficial effects of music therapy (Alayidh et al. 2025).

Overall, the existence of several behavioral treatments which have both the capability to broadly treat ASD as well as treat specific symptoms explain the prevalent status of this form of treatment as the mainstay ASD treatment. **Table 1** summarizes these behavioral treatments in the context of the other treatment options described in this article.

Table 1. Summary of treatment options for core and co-occurring symptoms with the relative effectiveness

	Symptom	Treatment Options	Effectiveness of treatment option	Reference
	<i>Speaking and communication in social settings</i>	Applied Behavior Analysis (ABA), Early Start Denver Model (EDSM) Music Therapy Oxytocin	ABA: Statistically significant improvements in all core symptoms after ABA treatment EDSM: after 2 years, 44% of children did not have core communication symptoms of Autism compared to 29% with standard behavior therapy. EDSM did not positively impact repetitive behavior pattern	ABA: Peterson et al. 2024, Anixt et al. 2024, Slocum et al. 2014 EDSM: Dawson et al. 2009 Music: Alayidh et al. 2025, Gassner et al. 2021

CORE SYMPTOMS			<p>Music Therapy: 9 clinical trials showed improvements in social skills and communication</p> <p>Oxytocin: Improvement in social responsiveness seen in certain studies and not seen in others; effect not consistent</p>	Oxytocin: Anagnostou et al. 2012
	<i>Repetitive behavior pattern</i>	ABA Bumetanide	<p>ABA improved repetitive behavior patterns</p> <p>Bumetanide improved symptoms from double-blind, placebo-controlled, phase 2 superiority trial in children</p>	<p>ABA: Peterson et al. 2024,</p> <p>Anixt et al. 2024, Slocum et al. 2014</p> <p>Bumetanide: Aishworiya et al. 2022, Baribeau et al. 2022</p>
CO-OCCURRING SYMPTOMS	<i>Hyperactivity & disruptive behavior</i>	Cannabinoids	A placebo-controlled, double-blind comparison of two oral cannabinoids found significantly improved measures of disruptive behavior	Aran et al. 2021
	<i>Lack of attention</i>	Music Therapy	Music therapy improved responsiveness	Alayidh et al. 2025
	<i>Aggression & Irritability</i>	Risperidone and Aripiprazole	56% decrease in irritability observed with risperidone	<p>Aishworiya et al. 2022, Aran et al. 2021</p> <p>McCracken et al.</p>

				2022
	<i>Anxiety</i>	Cognitive Behavior Therapy (CBT) Cannabinoids (CBD)	Rates of positive response >80% reported via CBT CBD shown to lower anxiety	CBT: Anixt et al. 2024, Wood et al. 2019 CBD: Aran et al. 2021

CHEMICAL PHARMACOLOGICAL AGENTS

Though behavioral treatments are currently the mainstay treatment for ASD, chemical pharmacological agents have also become common in the treatment of symptoms (Lord et al. 2022). Aishworiya et al. (2022) reported that 56% of all patients were prescribed at least one psychotropic medication, with 20% having been prescribed at least three (Aishworiya et al. 2022). Polypharmacy is also prevalent, with rates ranging from about 12% to 35% (9). Overall, treatment options are shaped by the underlying heterogeneity of ASD as well as by the varying comorbidities of the condition (Aishworiya et al. 2022). A summary of important drugs used to treat symptoms of ASD as well as their mechanism of action is provided in **Table 1** and described in detail below.

Drugs with Regulatory Approval: mainly for co-occurring symptoms

Until very recently, the United States Food and Drug Administration (US FDA) had only given regulatory approval to two antipsychotic drugs, risperidone and aripiprazole. These drugs treat irritability, a co-occurring symptom associated with ASD rather than a core symptom of ASD itself (Aishworiya et al. 2022, US Department of Health and Human Services). In the last few months, the drug leucovorin, also known as folinic acid, has now also been initiated for approval for use in ASD by the FDA. (FDA news release 2025, Hamilton J. 2026)

Risperidone, approved by the FDA in 2006, was the first drug approved to treat irritability from ASD (LeClerc and Easley 2015). A second-generation antipsychotic (SGA), risperidone blocks dopamine D2 receptors to some extent, but to a larger extent blocks serotonin receptors such as 5HT2A (McNeil et al. 2025), as explained in **Figure 2**. Risperidone is approved for patients between the ages of 5 and 16 (US FDA). In a study by McCracken et al. (2022), 101 children were randomly assigned either risperidone or placebo. Changes in Irritability scores (based on the Aberrant Behavior Checklist) and ratings on the Clinical Global Impressions — Improvement (CGI-I) scale were measured over eight weeks (McCracken et al. 2022). The study found a 56.9% reduction in Irritability scores in the risperidone group, compared to a 14.1% reduction in the placebo (McCracken et al. 2022). The study also found a 69% rate of a positive response (defined as a minimum of 25% decrease in the Irritability score and a rating of much improved

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or very much improved on the CGI-I scale) in the risperidone group compared to a rate of 12% in the placebo group (22). These results were found to be highly statistically significant (McCracken et al. 2022).

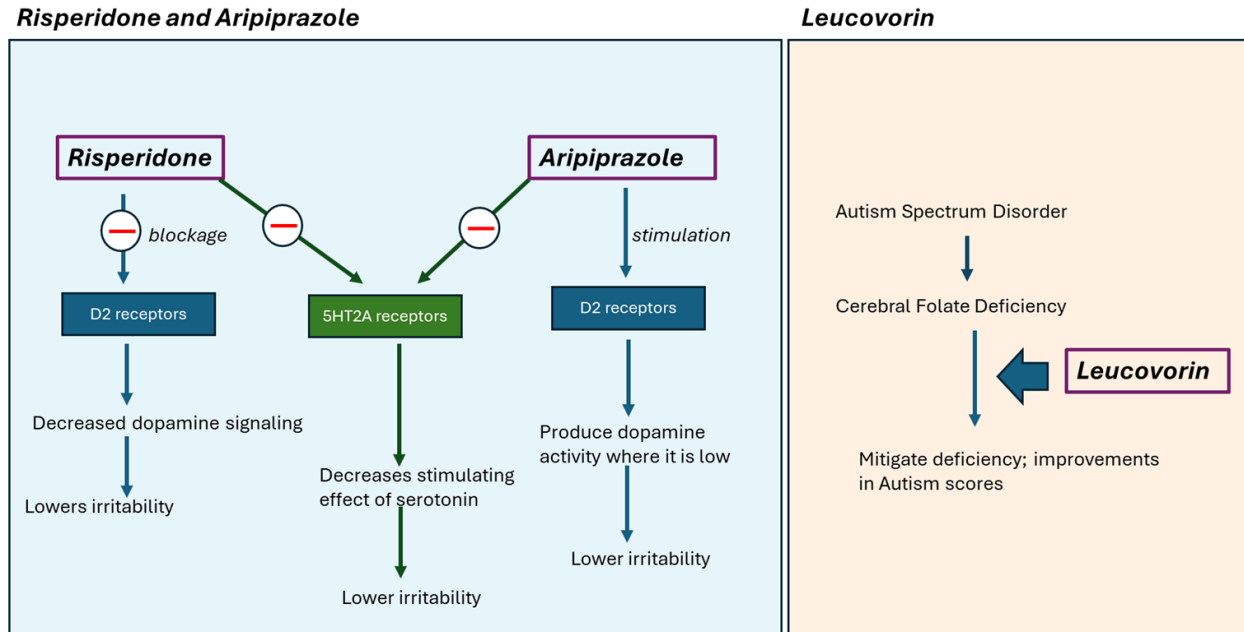


Figure 2. Mechanisms of action of FDA approved pharmacological treatments. Note that at this time, the US FDA has initiated approval for leucovorin while risperidone and aripiprazole are fully approved drugs.

Aripiprazole was later approved by the FDA in 2009 for the treatment of irritability in patients aged 6 to 17 years in ASD (LeClerc and Easley 2015, US FDA 2026). The mechanism of action of aripiprazole, though not fully known, may involve partial agonist activity at dopamine D2 receptors and serotonin receptor 5HT1A, and antagonist activity at 5HT2A receptors (LeClerc and Easley 2015), as summarized in **Figure 2**. A 2012 post hoc analysis by Varni et al. (2013) of two 8-week controlled clinical studies assessed the efficacy of aripiprazole compared to placebo (Varni et al. 2013). In total, 316 patients were randomly assigned to the aripiprazole group or the placebo group (Varni et al. 2013). Health-related quality of life was measured before and after the 8-week period using three Pediatric Quality of Life Inventory (PedsQL™) scales, measuring emotional functioning, social functioning, and cognitive functioning. Across all three scales, patients in the aripiprazole group were found to demonstrate significantly improved scores after the 8-week period compared to patients in the placebo group (Varni et al. 2013).

The US FDA recently initiated approval for leucovorin (folic acid), a folic acid analog, for use in ASD in September 2025, though not without controversy (FDA news release 2025, Hamilton 2026, NIH National Library 2024). The drug was intended for patients with cerebral folate deficiency (CFD) (Hamilton 2026). It has been suggested that a potential molecular mechanism for ASD is from

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abnormalities in folate metabolism, as CFD has been associated with ASD (see **Figure 2**). Studies have shown that antibodies known as FR α Ab interfere with the carrying of folate from the placenta to the brain through the primary carrier Fr α ; FR α Ab has been more commonly found in developing children with ASD than in typically developing children (Panda et al. 2024). This may explain the association of CFD with ASD, with these characteristics being especially common in individuals with Rett syndrome (Panda et al. 2024). Randomized control trials for folinic acid have been limited, though existing studies have shown potential to improve symptoms in children with ASD (Panda et al. 2024). A randomized control trial by Panda et al. (2024) found greater improvements in Childhood Autism Rating Scale score in the folinic acid group than in the placebo group (Panda et al. 2024). However, concerns have been raised that the rigor of trials for the use of folinic acid and its approval by the FDA have not been the level required for ASD (Hamilton 2026). Trials like one by Frye et al. (2018) which have shown improvements in ASD symptoms have also been scrutinized, with the study's first author Dr. Richard Frye remaining a controversial figure in the medical community (Hamilton 2026, Frye et al. 2018). The efficacy of such a treatment would require further knowledge of the role and prevalence of CFD in ASD, which is currently not fully known (Hamilton 2026). The use of leucovorin would also need to be tempered with the fact that the long-term tolerability profile of folinic acid has not yet been widely studied (Panda et al. 2024).

Other Drugs & research into agents to treat core ASD symptoms
Bumetanide

Due to the complex origin and development of ASD and the absence of well-defined molecular targets, efforts to develop drugs targeting the core symptoms of ASD themselves (more than just comorbid symptoms) have been met with significant difficulty (Wang et al. 2025). As previously mentioned, no officially approved interventions for addressing the core symptoms of ASD currently exist (Wang et al. 2025). Among various therapies which have been established to various extents, promising results have been variously shown, though not yet consistently (Wang et al. 2025). Bumetanide is a well-established loop diuretic, functioning by inhibiting sodium-potassium-chloride co-transporters NKCC1 and NKCC2 (Aishworiya et al. 2022, Baribeau et al. 2022). Gamma aminobutyric acid (GABA)-mediated synapses and their oscillations are altered in autism: GABA, which is typically an inhibitory neurotransmitter, can become excitatory because of elevated intracellular concentrations of chloride (Lemonnier et al. 2012). Bumetanide, with its inherent ability to decrease the intracellular chloride concentration, indirectly enhances GABAergic inhibition (Aishworiya et al. 2022, Baribeau et al. 2022), as explained in **Figure 3**. Two phase-2 placebo-controlled randomized control trials screened children for symptoms of ASD using several scales, such as the Social Responsiveness Scale (SRS) and the Childhood Autism Rating Scale (CARS) over a three-month treatment (Aishworiya et al. 2022, Baribeau et al. 2022, Lemonnier et al. 2012, Lemonnier et al. 2017). The first study examined 60 children from ages 3-11 with ASD or Asperger syndrome and found statistically significant improvements in ratings on various scales for most cases except those of very high severity (Lemonier et al. 2012). A later study examined 88 patients from ages 2-18 and found similar statistically significant improvements in CARS and SRS ratings among the bumetanide group as opposed to the placebo group (Lemonnier et al. 2017). Overall, both studies demonstrated the ability of bumetanide to improve a broad range of the core symptoms of ASD, with

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limited adverse effects (Aishworiya et al. 2022, Baribeau et al. 2022, Lemonnier et al. 2012, Lemonnier et al. 2017). That said, other trials have found fewer promising results in the improvement of ASD symptoms with bumetanide (Aishworiya et al. 2022, Baribeau et al. 2022). For example, another double-blind, placebo-controlled, phase 2 superiority trial in children with ASD did not show any treatment benefits on the core symptoms of ASD measured by the SRS, with only the repetitive behavior scale showing improvement (Aishworiya et al. 2022, Baribeau et al. 2022).

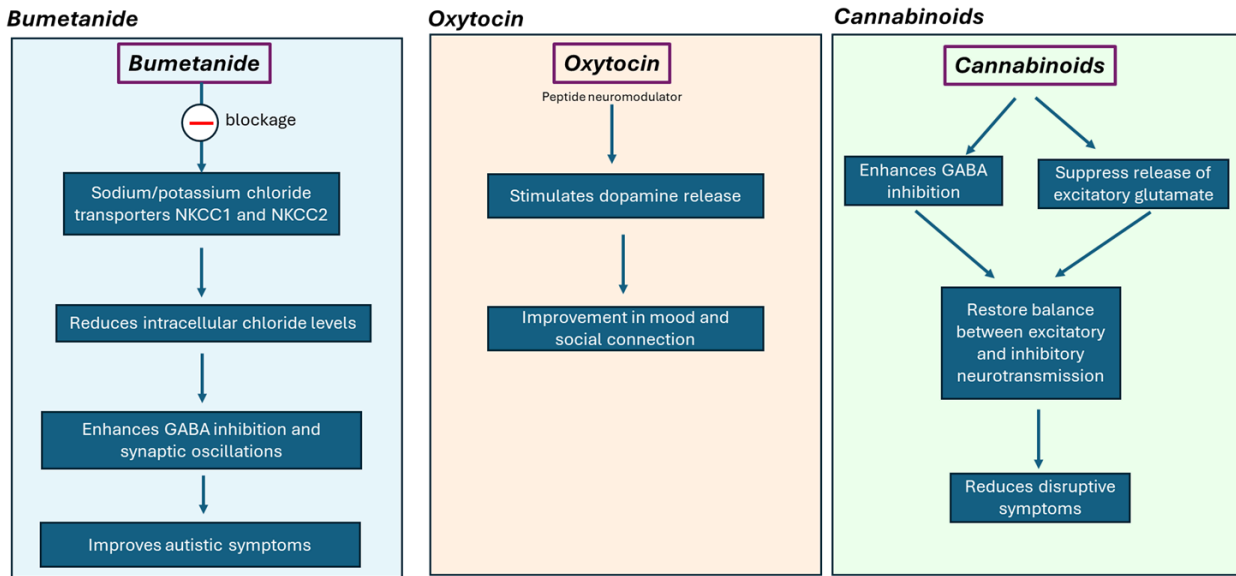


Figure 3. Mechanisms of action of emerging pharmacological treatments for Autism Spectrum Disorder

Oxytocin

Another targeted treatment for ASD is oxytocin, showing varying levels of efficacy in the treatment of ASD (Aishworiya et al. 2022, Baribeau et al. 2022). As explained in **Figure 3**: oxytocin, a peptide that serves as a neuromodulator in the human central nervous system, interacts with the dopaminergic system to modulate responses to external contextual social cues (Shamay-Tsoory et al. 2016). Attention has been brought to the therapeutic applications of oxytocin to conditions characterized by aberrant social behavior like ASD, though still considering the differing baseline conditions of various individuals (Shamay-Tsoory et al. 2016). It has been shown that intranasal oxytocin can lead to increased activation in regions of the brain known to be involved in handling social-emotional information and enhanced connectivity between nodes of the brain's reward and socioemotional processing systems (Aishworiya et al. 2022).

Several shorter-term studies using smaller samples have been conducted to assess the efficacy of oxytocin for ASD (Aishworiya et al. 2022). Several such trials have shown improvements in various core symptoms of ASD, including repetitive behaviors, social reciprocity, and emotion recognition (Aishworiya et al. 2022). For instance, one such trial by Anagnostou et al. (2012) evaluated the

effectiveness of intranasal oxytocin versus a placebo on 19 adults with ASD over a duration of six weeks (Anagnostou et al. 2012). On various scales measuring common ASD symptoms and other metrics, improvements were found in measures of social cognition and quality of life, though not in any of the primary outcomes (Anagnostou et al. 2012). Similarly, other short-term studies failed to demonstrate any oxytocin specific improvements in the core ASD symptoms of repetitive behavior or social responsiveness (Aishworiya et al. 2022). Another short-term study by Moerkerke et al. (2023) examined the role of intranasal oxytocin administration in children with ASD, comparing results after four weeks with those of a placebo (Moerkerke et al. 2023). The study found increased feelings of secure attachment among patients. Additionally, there was reduced oxytocin receptor gene DNA-methylation among those with heightened oxytocin levels, indicating the stimulation of the endogenous oxytocinergic system among patients (Moerkerke et al. 2023). Long-term studies of oxytocin administration have also found mixed results among patients with ASD (Aishworiya et al. 2022). For example, a recent trial examined the long-term effects of intranasal oxytocin administration on 40 adult men with ASD for four weeks by analyzing their symptoms at follow-up sessions four weeks and one year after initial treatment (Anagnostou et al. 2012). Though some statistically significant improvements in repetitive behaviors and avoidance of others were uniquely found in the oxytocin group (as opposed to those who received a placebo), there were no differences in measures of social responsiveness (Anagnostou et al. 2012).

Cannabinoids

The consumption of cannabis has been reported to enhance interpersonal communication and decrease hostile feelings (Aran et al. 2021). Among the main components, or phytocannabinoids, of the cannabis plant are Δ^9 -tetrahydrocannabinol (THC) as well as cannabidiol (CBD) (Aran et al. 2021). Several reports have suggested a variety of benefits for cannabinoids in their use to modify the endocannabinoid system in some capacity (Baribeau et al. 2022). Unlike THC, which activates the type-1 cannabinoid receptor (CB1R) and is psychoactive, leading to anxiety and psychosis, CBD allosterically modulates the CB1R. The latter is not psychoactive; has a relatively high toxicity threshold; and is shown to have numerous therapeutic effects including treatment of anxiety, pain, nausea, and motor deficits (Aishworiya et al. 2022, Aran et al. 2021). Through various mechanisms, CBD has been shown to improve the balance in inhibitory and excitatory transmission and help restore neuronal function and synaptic plasticity in patients with ASD (Aishworiya et al. 2022), as described in **Figure 3**. A placebo-controlled, double-blind comparison of two oral cannabinoids containing varying ratios of THC and CBD found significantly improved measures of disruptive behavior in the cannabinoid containing mostly CBD (whole plant extract) compared to the placebo. However, it did not find significant differences between the two for other measures of ASD symptoms (Aran et al. 2021).

Many chemical pharmacological treatments do not have widespread use in ASD treatment, with the currently used treatments generally only treating co-morbid symptoms. Drugs treating core symptoms, while they do show some promising results at times, have in general not yet reproducibly been shown to consistently improve symptoms.

GENE THERAPY: A PERSONALIZED TREATMENT FOR INDIVIDUALS WITH MONOGENIC FORMS OF ASD

Gene therapy is an emerging treatment for ASD which has shown promising results and has the potential to be a highly personalized option. With ASD appearing to have a genetic component, its symptoms may also be reversible postnatally, making gene therapy a relevant treatment which may be effective in the reduction of common symptoms (Benger et al. 2018). Broadly, gene therapy is built on the possibility of introducing a normal gene or protein into the central nervous system (CNS) where a mutation is known (Aishworiya et al. 2022). As explained in **Figure 4**, this normal gene is introduced into a laboratory virus which is made incapable of reproduction. Cells from an ASD patient are isolated and are mixed with this virus, which then enters these cells and integrates the normal gene into the genome of the isolated patient cells. These patient cells with the normal gene in their genome are then reintroduced into the ASD patient body. These nucleic acid polymers delivered into target cells may be able to repair, replace, augment, or silence any genes of interest (Ay and Reinisch 2025, Benger et al. 2018). If gene therapies are developed such that the genome is permanently altered, symptoms of ASD can be alleviated with few treatments (Weuring et al. 2021).

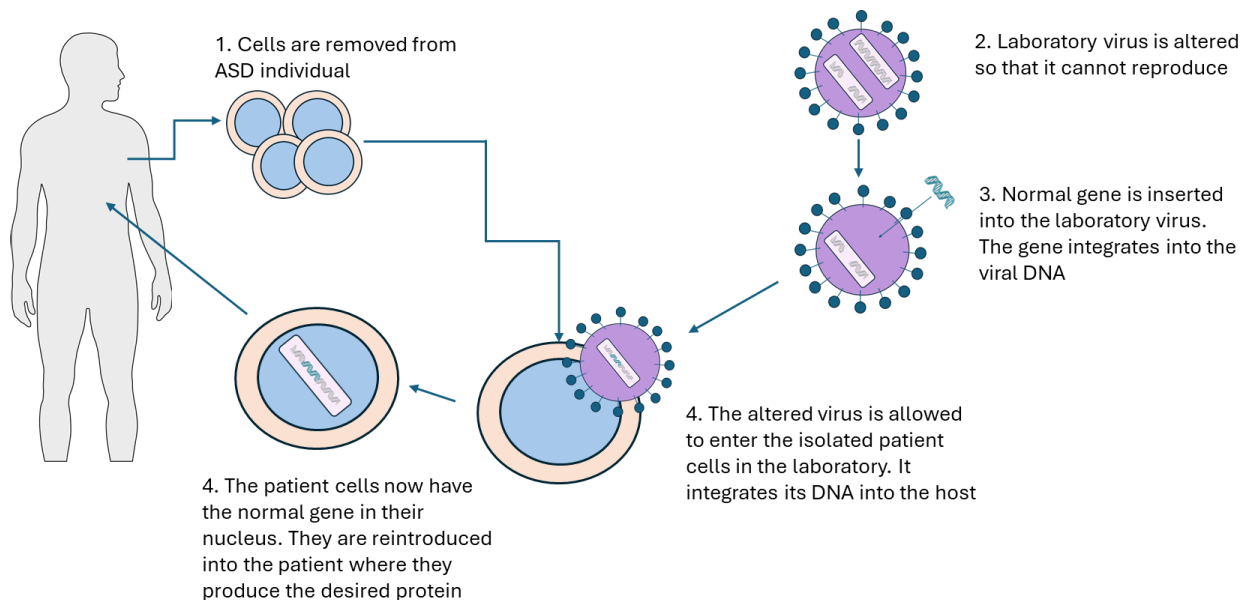


Figure 4. How gene therapy is being considered as a treatment for Autism Spectrum Disorders

Gene therapy is still in a relatively early stage of development as a treatment, with the therapy not currently approved regulatorily for patients to utilize (Aishworiya et al. 2022). The primary challenge in the development of and a potential inherent limitation in gene therapy as a treatment for ASD has been the genetic heterogeneity of this condition (Benger et al. 2018). It is often not possible to attribute ASD to

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a single causative mechanism, including due to new findings in immune dysfunction and epigenetics in certain cases (Benger et al. 2018). This heterogeneity could preclude the use of gene therapy outside of monogenic forms of ASD, which are conditions driven by a single genetic defect (Benger et al. 2018). It is often only in these forms of ASD, which account for about 5% of ASD cases, that genetic models can be clearly developed, with information like the genotype to phenotype pathway and the causative protein of the condition being more well-understood. That said, considering the relatively widespread prevalence of ASD in the global population, such treatments for ASD are still promising treatments for the millions of individuals who have monogenic forms of ASD (Benger et al. 2018). Furthermore, new methods of identifying risk genes for ASD to develop a clear pathogenesis of ASD beyond individual risk genes, such as through High-content analysis, may allow the effectiveness of gene therapy to be enhanced (Arta et al. 2025).

For monogenic ASD, gene therapy strategies include gene replacement, RNA knockdown, and gene editing (Benger et al. 2018). Gene editing, which is made possible by the new advances including the development of clustered regularly interspaced short-palindromic repeat (CRISPR)/Cas9 technologies, has attracted significant attention in recent years (Ay and Reinisch 2025, Benger et al. 2018, Kantor et al. 2025). In regard to the means of delivery of gene therapy into the central nervous system, the adeno-associated virus (AAV) has been utilized as a primary vector for gene therapy of disorders in the central nervous system (CNS) (35, 38). Benefits of AAV include its high transduction efficiency, low immunogenicity and toxicity, its ability to persist in episomal form, and exceptional tissue specificity (Benger et al. 2018, Kantor et al. 2025).

Research has also indicated potential use of AAV in delivering CRISPR-based modalities into the brain for gene editing (Kantor et al. 2025). For example, a recent preclinical study attempted to restore various insufficiencies in the sodium voltage-gated channel alpha subunit 2 gene (SCN2A) (Ghosh et al. 2023). The study used CRISPR activation technology to target SCN2A-associated autism in mice to restore SCN2A function by injecting a recombinant AAV construct into haploinsufficient mice and found an increase in SCN2A expression after thirty days postnatally, further demonstrating impact that CRISPR technology can have on the effectiveness of gene therapy (Ghosh et al. 2023).

Overall, advances in the ability to model disorders in animals have allowed some of the first preclinical studies in monogenic ASD (Benger et al. 2018). Some rodent models have demonstrated quantifiable social and communicative behavioral traits, though there is inherent difficulty in modeling the phenotypic effects of ASD symptoms in animals and understanding the analogous effects of treatments on humans following animal studies, leading many potential therapies to struggle to transition from preclinical trials (Benger et al. 2018). It is often difficult to incorporate and analyze various environmental influences, including psychosocial factors, in animal models (Benger et al. 2018). These issues in creating reproducible and robust animal models for the effects of these treatments further complicate the modeling of polygenic forms of ASD and highlight the importance of considering gene-environment interactions in ASD treatment (Benger et al. 2018). That said, in monogenic conditions with autistic features including Rett syndrome, fragile X syndrome, Angelman syndrome (AS), and tuberous sclerosis, the identification of the nature and function of causative genes has allowed the progression of early-stage trials towards the

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use of gene therapy for monogenic ASD (Benger et al. 2018). For example, a phase 1 trial has shown promising results for the treatment of AS (Hipp et al. 2025). AS is caused by a deletion or mutation in the gene encoding the ubiquitin-protein ligase E3A (UBE3A) (Hipp et al. 2025). The trial attempted to use an antisense oligonucleotide known as Rugosersen in children aged 1-12 to reinstate UBE3A by de-repressing the silenced paternal allele (Hipp et al. 2025). Not only did the trial meet the primary endpoint of safety and tolerability, it also showed signs of improvement in AS symptoms through a variety of measures (Hipp et al. 2025). Results like these in monogenic conditions like ASD can provide a basis for preclinical and perhaps even clinical studies of gene therapy in monogenic ASD itself (Aishworiya et al. 2022, Benger et al. 2018).

While increasing research towards the use of gene therapy in ASD is still in an early stage, indications do exist towards the efficacy of such treatments in monogenic forms of ASD.

ANALYZING THE THREE TREATMENT APPROACHES

This review considered three forms of treatment for ASD, including behavioral treatments, chemical pharmacological (drug) treatments, and treatments based on gene therapy. These three treatment categories are summarized in **Figure 5** along with the ASD symptoms they are intended to address. Behavioral treatments are the current mainstay treatment of ASD. Improvements in various ASD symptoms have been shown in both broad interventions such as applied behavioral analysis (ABA), the Early Start Denver Model (ESDM) and Music Therapy (MT), as well as in focused interventions on a variety of scales. That said, these treatments have not necessarily and universally been shown to improve diagnostic status in all measures. Regarding chemical pharmacological treatments, only two treatments, aripiprazole and risperidone, are currently approved by the FDA for ASD-related use and treat the co-morbid symptoms of irritability. Other established and developing treatments, including oxytocin, bumetanide, and cannabinoids, have shown varying efficacy in treating intended symptoms. Treatments based on gene therapy have more recently emerged but are in general limited to monogenic forms of ASD and ASD-related conditions, which comprise a minority of ASD cases, since the heterogeneity of ASD currently precludes the effective treatment of polygenic forms. For monogenic forms, however, recent technologies and developments, such as CRISPR/Cas9 and improvements in animal modeling of disorders, have allowed further development of these treatments. Some preclinical, and even early-stage clinical trials have occurred and have shown promising results.

Since different treatments have different inherent purposes in addressing aspects of ASD, the forms of ASD and the symptoms that are best treated by any given treatment varies. Therefore, these treatments can treat the core symptoms of ASD in a varied manner, which include restricted patterns of behavior and deficits in social interaction and communication. To start, all the behavioral treatments discussed in this review appear to be able to improve the core symptoms of challenges in social communication but have not shown appreciable improvements with respect to the core symptom of repetitive behavior. In regard to chemical pharmacological treatments, there is inconclusive and often contradictory evidence as to

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whether core symptoms are effectively treated. As an example, the drug oxytocin, between different short-term studies, showed statistically significant improvements in core symptoms of ASD in some but showed no improvements in core ASD symptoms in others; similarly, long-term studies have also found mixed results. Furthermore, no drugs which treat core symptoms of ASD have been approved by the FDA. Risperidone and aripiprazole, the only FDA-approved treatments for use in ASD patients, only treat the co-occurring symptom of irritability. Treatments based on gene therapy are in early stages of development, so the extent to which core symptoms of ASD can be treated is currently unclear, though preliminary signs of improvement seen in the success of early gene therapy models in altering causative genes in applicable diseases suggest promising potential utility of this treatment in this regard.

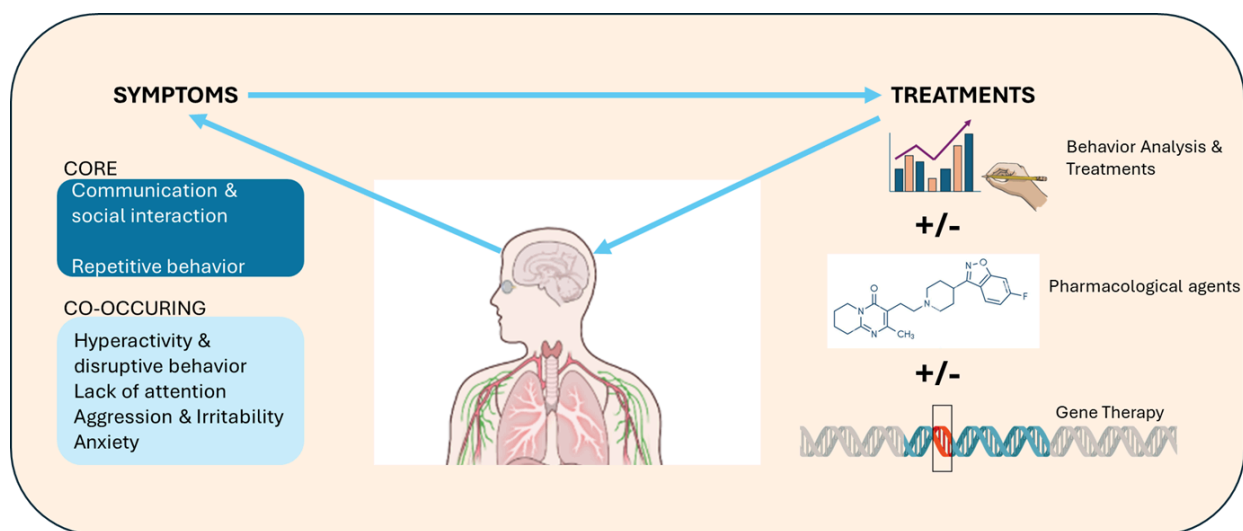


Figure 5. Overall summary and personalized treatment options for ASD

Towards creation of additional personalized treatment strategies

Age and gender can play a role

Knowing the use of various treatment options for ASD as it relates to how they address both core and co-occurring symptoms leads to the question of how effective treatment strategies can be developed to deliver treatment to individual patients. The heterogeneity of ASD is seen in various different factors which contribute to differences in treatment effectiveness between different individuals. For example, age is a common factor that influences ASD treatment, with treatment administered at early ages generally thought of as being more effective for ASD treatment, with the brain still being at an early stage of development (Anixt et al. 2024, Towle et al. 2020). While there has not necessarily been universal support for this idea, young children with ASD still benefit from increased support that is gained through the early identification of symptoms, educational services that may benefit them, and the ability to create tailored treatments (Towle et al. 2020). In addition, gender, a significant factor in diagnosis, where estimates place the gender divide at 4 males diagnosed with ASD for every female diagnosed, may also be a potentially significant factor in treatment options (Masi et al. 2017, McVey et al. 2019). Due to the reduced level of

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ASD diagnosis among females, little research has been done on the effect of ASD treatment on females (McVey et al. 2019). Many studies of ASD treatments, including those referenced in this study, focus primarily or exclusively on the effects of the treatments on males. While some treatments, such as the PEERS Social Skills Intervention, showed no differences between males and females in treatments, it is still overall not clear how the effectiveness of ASD treatments will vary by gender (McVey et al. 2019). Other factors such as severity of symptoms and genetic history also contribute to the selection of treatment options to be administered (Masi et al. 2017). Additionally, accessibility and use of treatments is determined by socioeconomic factors and cultural predispositions relating to treatment (Masi et al. 2017). Individuals with ASD may also struggle to manage their symptoms due to inherent factors like limited language repertoire, low cognitive function, and uncertain symptoms complicating treatment options (Lord et al. 2022).

Treatment approaches can be combined to create an individualized plan

Another personalized strategy that may be utilized to effectively treat ASD symptoms is to combine different treatments for ASD, which is also depicted in **Figure 5**. This is due to the multifaceted nature of ASD symptoms, with up to 68% of ASD patients exhibiting co-occurring symptoms in addition to core symptoms (London and Yoo 2021). Personalized treatment plans need to be developed to address the unique presentation of symptoms in each patient (London and Yoo 2021). From this, the overall purpose of combining treatments would be to provide a combined benefit by selectively treating undesirable symptoms (London and Yoo 2021). Combining behavioral treatments such as applied behavioral analysis and pharmacological treatments is relatively common to treat ASD symptoms, though limited research currently exists regarding the effects and possible benefits of combining these treatments (London and Yoo 2021). Existing studies regarding the combination of treatments have investigated the effect of combining the FDA-approved treatments for ASD, including risperidone and aripiprazole, with behavioral therapies (London and Yoo 2021). While results of such studies have not always pointed to effectiveness of combined treatments, improvements have still commonly been found, with the effects of one treatment, such as improved behavior from risperidone, allowing for better results from the other treatment, such as increased readiness to engage in the social interaction and communication that comes with ABA (London and Yoo 2021). One study which combined bumetanide with ABA, as well as another study which combined melatonin and cognitive behavioral therapy, also found improvement from the combined treatments, at least in the short term (London and Yoo 2021).

Ethical considerations must be taken into account

Behavioral treatments like applied behavioral analysis (ABA) have been criticized for the common premise of needing to make children with ASD indistinguishable from their “normal” peers who do not have ASD; this precedent was set at the beginning of the development of ABA and expectations of desired behaviors were often harshly enforced with punishment (Garey 2025). Though many ABA practitioners nowadays attest to using improved methods of treatment based on positive reinforcement, the idea that certain behaviors need to be changed and that differences between children need to be eliminated, especially in less severe cases of ASD, remains controversial, especially among those not

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wanting the neurodiversity of the individual with ASD to be lost (Garey 2025). Correlations between treatments which lead to camouflage with the neurotypical population and poor mental health as well as suicidality have also been found (Cassidy et al. 2018). In general, findings like these emphasize the relevance of considering the ethical implications of treatments given to patients with ASD, even in treatments which may theoretically seem viable.

FUTURE DIRECTIONS AND CONCLUSION

Behavioral treatments, though the current mainstay of ASD treatments and often showing promising results, need to be improved to address the growing ethical considerations and implications of these treatments, increasing the relevance of evidence-based, focused behavioral interventions. This will allow behavioral treatments to effectively address symptoms that are in need of improvement and those which are known to be effectively treated by such treatments. For pharmacological treatments, more research continues to be done and will need to be done, as the effectiveness of these treatments at treating ASD symptoms is not clear. As pharmacological treatments which have currently shown at least some promising results continue to be tested for reproducible results, the increasing clarity on the symptoms that can be treated, which include both core and comorbid symptoms, will lead to increased understanding on which treatments treat which symptoms. Regulatory approval of a wider range of treatments is also expected, as evidenced by US FDA's recent *initial* approval of the drug leucovorin for ASD. While this demonstrates an increasing trend of more treatment options being considered for approval of ASD treatments, it also highlights the necessity of adequately and clearly understanding the effects of treatments before they are approved for widespread use in ASD as demonstrated by the cautioning against leucovorin by many autism researchers. In any case, regulatory approval of ASD treatments should not be misconstrued as the identification of a "cure" for ASD, as no currently developed treatment is yet capable of and reproducibly shown to universally treat the root causes of ASD, with the limited exception of gene therapy. That said, while gene therapy treatments are limited in the overall scope for treatment of ASD, they are showing promising results in relation to the target population of those with monogenic ASD, potentially becoming a mainstay treatment in the more distant future. All these factors will allow for the more effective combining of various treatments and the development of improved individual treatment strategies for the diverse and heterogeneous population with ASD.

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*Online resource, subject to change and may not be accessible at a later stage.

GLOSSARY

Adeno Associated Virus (AAV)

Angelman Syndrome (AS)

Applied Behavior Analysis (ABA)

Assess and Monitor (A/M)

Assessment of Basic Language and Learning Skills (ABLLS)

Autism Diagnostic Observation Schedule (ADOS)

Autism Spectrum Disorder (ASD)

Cannabidiol (CBD)

Central Nervous System (CNS)

Cerebral Folate Deficiency (CBD)

Childhood Autism Rating Scale (CARS)

Clinical Global Impressions – Improvement (CGI – I)

Clustered Regularly Interspersed Short Palindromic Repeat (CRISPR)

Cognitive Behavior Therapy (CBT)

Early Start Denver Model (ESDM)

Gamma Aminobutyric Acid (GABA)

National Institutes of Health (NIH)

Naturalistic Developmental Behavioral Interactions (NDBI)

Pediatric Quality of Life Inventory (PedsQL)

Second Generation Antipsychotic (SGA)

Sodium Voltage Gated Channel Alpha Subunit 2 Gene (SCN2A)

Social Responsiveness Scale (SRS)

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Ubiquitin Protein Ligase E3A (UBE3A)

United States Food and Drug Administration (US FDA)

Verbal Behavior Milestones Assessment and Placement Program (VBMAPP)

Δ 9-tetrahydrocannabinol (THC)