American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Psychopharmacological Interventions for Autism Spectrum Disorder: A 5-Year Review

Yulu Han[1]*, Wang Haotian[2], Fanzi Hao[3] and Yumin Jiang[4]

[1]*Qingdao Medical College, Qingdao University, Qingdao, Shandong, China*

[2]*Pharmacy Department, 910th Hospital, Quanzhou, Fujian, China*

[3]*Nanning College of Technology, Nanning, Guangxi, China*

[4]*Department of Hepatobiliary and Pancreas, Affiliated Hospital of Qingdao University, Qingdao, Shandong, China*

***Corresponding author:** Yulu Han, Qingdao Medical College, Qingdao University, Qingdao, Shandong, China.

To Cite This article: *Yulu Han*, Wang Haotian, Fanzi Hao and Yumin Jiang, Psychopharmacological Interventions for Autism Spectrum Disorder: A 5-Year Review. Am J Biomed Sci & Res. 2026 30(4) AJBSR.MS.ID.003938,* **DOI:** 10.34297/AJBSR.2026.30.003938

Received: March 08, 2026; **Published:** March 13, 2026

Abstract

While behavioural therapies remain the primary approach for managing Autism Spectrum Disorder (ASD), there has been a notable increase in specialized interventions that address the neurophysiological aspects of ASD in recent years. Although no medications have been officially approved for the direct treatment of the core symptoms of autism, numerous studies have investigated the efficacy of various substances, including cannabinoids and other pharmacological agents. This review provides an overview and comparison of the current psychopharmacological treatments available for ASD, focusing on traditional psychotropic drugs such as risperidone and aripiprazole, alongside newer agents like cannabidiol and bumetanide. The study examines the mechanism of action, clinical application status, efficacy evaluation, and related challenges while offering references to support the advancement of clinical treatment.

Keywords: Atypical Antipsychotics, Autism Spectrum Disorder, Mood Stabilizers, Pervasive Developmental Disorders, Psychopharmacology

Introduction

Autism Spectrum Disorder (ASD) constitutes a multifaceted neurodevelopmental condition rooted in biological factors, impacting approximately 1 in 44 individuals [1]. It affects multiple aspects of development, including behaviour, problem-solving abilities, self-care skills, and social communication. The symptoms of ASD vary widely in type and severity among individuals, influenced by factors such as age, cognitive abilities, language skills, and co-occurring conditions. The most recent update of the Diagnostic and Statistical Manual (DSM-5) characterizes ASD by deficits in social communication and interaction, as well as restricted, repetitive patterns of behaviour. Social communication deficits include difficulties in social-emotional reciprocity, challenges in nonverbal communication, and problems in forming and maintaining relationships [2]. Additionally, restricted, repetitive, and stereotypical patterns of behavior are exhibited through unusual repetitive actions or behaviors, limited interests, a strong insistence on consistency, and a rigid commitment to routines [3, 4]. ASD is often accompanied by co-occurring mental health and medical conditions, including Attention Deficit Hyperactivity Disorder (ADHD), anxiety, depression, intellectual disabilities, speech and language impairments, sleep disturbances, and sensory processing difficulties [5, 6]. These co-occurring conditions can significantly impact the overall functioning and quality of life of individuals with ASD, complicating the identification, diagnosis, and clinical treatment [7].

Traditional approaches to managing medical conditions primarily focus on pharmacological therapies. However, despite years

of research into ASD, the prevailing evidence supports behavioral (non-pharmacological) interventions as the cornerstone of treatment for core ASD symptoms. One factor contributing to the limited effectiveness observed in numerous treatment studies is the diverse etiology encompassed by the broad classification of ASD. Some investigations have addressed this complexity by categorizing participants based on genetic backgrounds or phenotypic characteristics. the objective of this paper is to provide an updated overview and comparison of the current psychopharmacological options available for ASD, alongside various therapeutic subtypes, including both established and novel treatments that may become standard care in the coming years based on scientific findings.

According to system evaluation and management analysis instructions (PRISMA), systematic literature access was applied in January 2025. When the registration number 42024617873, this research is recorded in the initial database of the original system (flowering) international assessment. The search was conducted across four databases: MEDLINE/PubMed, ScienceDirect, Scientific Electronic Library Online (SciELO), and Web of Science. Using keywords such as "autism," "autism spectrum disorder," and "psychopharmacology", we searched 731 papers published between 2019 and January 2025. Subsequently, we performed an additional screening of reserved double-blind placebo-controlled clinical trials, which yielded 7 studies (Figure 1). In this analysis, we focus on psychopharmacological treatments such as risperidone, aripiprazole, bumetanide, and cannabidiol, all of which exhibit significant efficacy and are generally available to clinicians either currently or shortly (Figure 1).

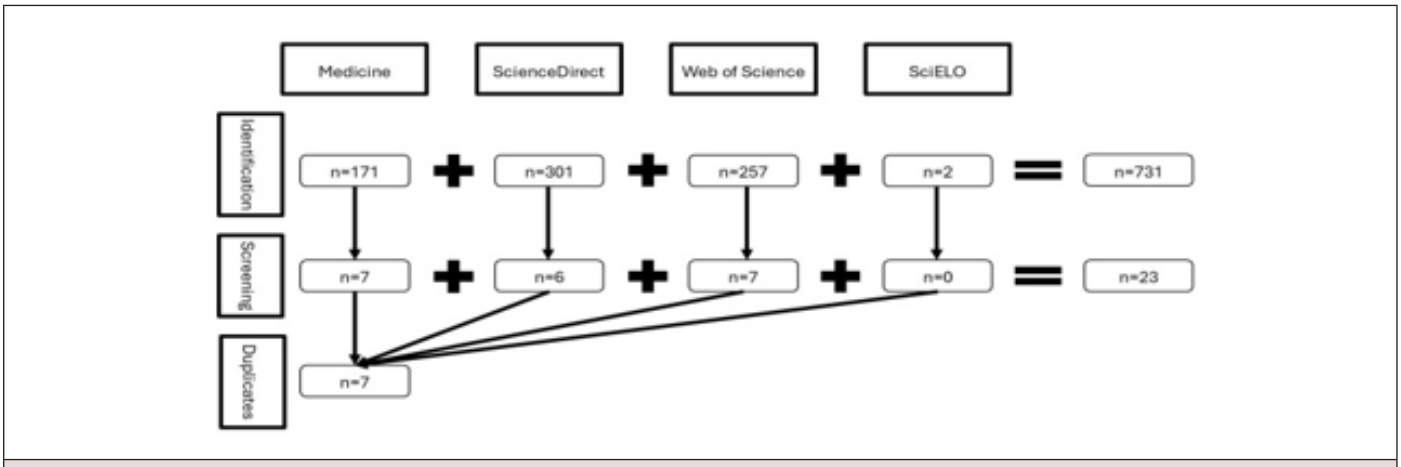

Figure 1: Study selection flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for psychopharmacology in autism.

Established Psychopharmacological Treatments

Risperidone

Risperidone is classified as an atypical antipsychotic and is commonly used to address irritability and related behavioral issues in children and adolescents diagnosed with ASD. The therapeutic benefits of the drug primarily arise from its effects on neurotransmitter systems, specifically targeting serotonin and dopamine pathways. The primary mechanism of action of risperidone involves the antagonism of dopamine D2 and serotonin 5-HT2A receptors. This combined action is particularly significant as it helps to normalize the neurotransmitter systems that often exhibit dysregulation in individuals with ASD [8,9]. Risperidone is one of the few medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of irritability associated with ASD in children and adolescents aged 5 to 16. Clinical trials have demonstrated its efficacy, indicating that risperidone significantly reduces disruptive behaviors compared to a placebo, with notable improvements in irritability, aggressive behavior, and self-harming tendencies [9-11]. A meta-analysis investigating pharmacological interventions for ASD found that both risperidone and aripiprazole significantly impacted core symptoms, which include difficulties in social communication and repetitive behaviors [12]. Additionally, the pharmacokinetic properties of risperidone, as well as its active metabolite 9-hydroxy risperidone, are essential for its effectiveness. Research on therapeutic drug monitoring indicates that keeping plasma concentrations within a specific range can improve treatment results and reduce adverse effects [10]. It is essential to recognize that individual responses to risperidone can differ markedly, possibly due to genetic factors that affect drug metabolism and receptor sensitivity [9,13].

Notwithstanding its endorsement and proven effectiveness, administering risperidone to children with ASD raises certain concerns. This medication may result in side effects such as weight gain, drowsiness, and elevated prolactin levels, potentially requiring thorough monitoring and management [10]. Nonetheless, the proof regarding its effectiveness in alleviating core symptoms re-

mains regarded as initial, and the regular prescription of risperidone for these symptoms is not consistently advised [12].

Aripiprazole

Aripiprazole, classified as an atypical antipsychotic, has garnered attention for its potential therapeutic benefits in managing behavioral dysregulation associated with ASD in younger populations. The drug operates through a multifaceted mechanism, primarily interacting with various neurotransmitter systems, particularly the dopamine and serotonin pathways [9,14]. Furthermore, studies indicate that aripiprazole may enhance the levels of Brain-Derived Neurotrophic Factor (BDNF) and phosphorylated cAMP Response Element-Binding Protein (p-CREB) in neuronal cells. These factors play a critical role in neuronal survival, synaptic plasticity, and overall cognitive performance [14,15].

Aripiprazole, FDA-approved 2009, shown effective/safe via trials, preferred for ASD behavioral issues [9,15]. Recent randomized controlled trials indicate that aripiprazole effectively reduces symptoms such as irritability, hyperactivity, inappropriate verbal communication, and repetitive behaviors within this population [16]. A clinical research study compared the effects of aripiprazole and risperidone over 10 weeks, revealing that both medications led to substantial improvements in irritability. Notably, the aripiprazole group experienced considerably less weight gain, which is a critical consideration given the potential side effects associated with weight gain in younger patients [16-18].

Aripiprazole's benefits require noting hypertension risk, as in an ASD child's case [19]. This underscores the necessity for careful monitoring of blood pressure in pediatric patients receiving treatment with aripiprazole. Research has associated aripiprazole with a variety of adverse effects, including weight gain, sedation, excessive salivation, and tremors [20]. Additionally, it has been observed that aripiprazole may increase appetite, potentially exacerbating this negative outcome, whose effect could involve alterations in glucose and lipid metabolism, thereby increasing the risk of developing diabetes and cardiovascular issues over time [13]. Consistent evaluation of metabolic indicators is crucial for children undergoing long-term treatment with aripiprazole. Parents and caregivers must work closely with healthcare professionals to ensure that any adverse effects are promptly identified and managed.

Off-label use of risperidone/aripiprazole beyond FDA-approved ASD irritability raises ethics concerns due to untested safety/efficacy [19]. The ethical implications of the pharmaceutical industry's role in promoting medications like risperidone cannot be overlooked. Marketing practices may prioritize profit over patient welfare, leading to the over-prescription of medications without adequate consideration of their long-term effects on children with ASD [21].

Emerging Targeted Treatments with a Possible Role in ASD

Bumetanide

Bumetanide, a loop diuretic, has been explored for its potential therapeutic benefits in ASD due to its capacity to influence the Excitatory-Inhibitory (E-I) balance in the brain. As illustrated in Figure 2, the primary mechanism by which bumetanide exerts its effects involves the inhibition of the Sodium-Potassium-Chloride Cotransporter 1 (NKCC1), a transporter that plays a crucial role in regulating intracellular chloride levels, which subsequently impacts GABAergic signaling, a key inhibitory neurotransmitter system in the brain [22,23]. By inhibiting NKCC1, bumetanide reduces intracellular chloride concentrations, which shifts the effect of GABA from excitatory to inhibitory. This alteration may alleviate certain symptoms associated with ASD, including social impairments and repetitive behaviors [24].

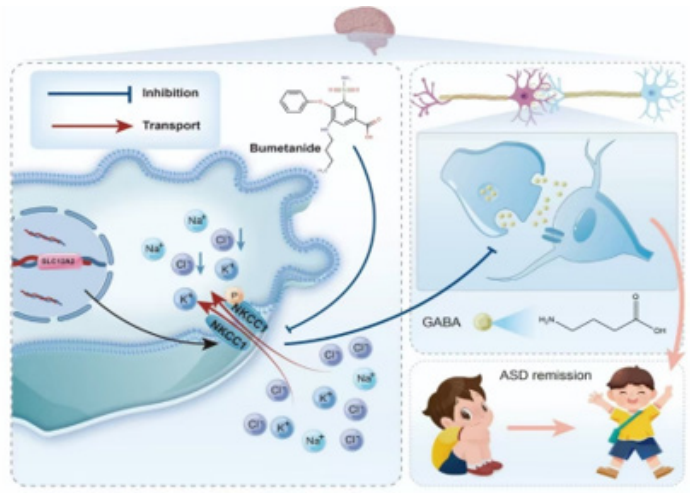

Figure 2: The mechanism of bumetanide in the treatment of autism.

Recent clinical research has emphasized the effectiveness and safety of bumetanide in addressing core symptoms of ASD, especially among children aged 3-6 years, with tablet formulations and interventions lasting three months. For instance, a clinical trial demonstrated that individuals treated with bumetanide experienced significant reductions in symptom severity, along with changes in GABA/glutamate ratios in the brain, suggesting a neurobiological basis for the observed behavioral changes [22]. A case report described a child diagnosed with ASD who exhibited significant improvement in symptoms following bumetanide therapy, while prior treatment with Vitamin D had not produced positive results. This case underscores the potential of bumetanide to target various mechanisms involved in the pathophysiology of ASD [25]. Currently, two Phase III trials are underway to evaluate the efficacy and safety of bumetanide in children and adolescents diagnosed with ASD, the results of which may pave the way for the first pharmacological intervention specifically aimed at enhancing social reciprocity and reducing repetitive behaviors in children affected by ASD [26]. A meta-analysis of nine randomized controlled trials (RCTs) involving 1,036 participants showed that bumetanide significantly improved overall core symptoms of ASD, particularly in sub-domains including relation to inanimate objects, adaptation to environmental changes, auditory response, and anxiety [27].

Despite these encouraging results, the application of bumetanide in clinical settings encounters several challenges. Some studies have indicated that bumetanide treatment could improve factors such as irritability and social behavior [28-30]. However, in a recent study, bumetanide did not significantly affect the core symptoms of ASD, including repetitive behaviors and challenges in social communication. This finding suggests that bumetanide may not address all facets of ASD [31]. Clinical trials generally indicate that participants tolerate bumetanide well. However, it is important to recognize that the existing studies predominantly consist of open-label trials with relatively small sample sizes, which may not adequately represent the full spectrum of side effects that could arise in a larger population [29,32]. Bumetanide may cause common side effects associated with diuretics, such as electrolyte imbalances, dehydration, and potential alterations in renal function. [33]. Moreover, the pharmacological characteristics of bumetanide indicate potential systemic effects that extend beyond its functions in the central nervous system. For instance, it has been proposed that bumetanide might engage with the immune system, which may introduce further considerations about its safety and tolerability in children diagnosed with ASD [28]. More about the clinical studies are described in Table 1. Bumetanide shows promise as a potential treatment for ASD, particularly in improving social behaviors and reducing symptom severity. However, its application in clinical settings faces several challenges, including inconsistent results across studies and potential side effects. Future research, particularly large-scale, well-controlled trials, is needed to fully understand the efficacy and safety profile of bumetanide in ASD. Additionally, further investigation into the mechanisms underlying its therapeutic effects and potential interactions with other biological systems is warranted.

Table 1: Clinical Trial: Bumetanide and Cannabidiol for Autism Treatment.

Test Form		Drug Name	Dose	Sample Size	Experimental Group Sample	Control Group Sample	Improved Outcome Measure	Results and Treatment Effectiveness
Therapy Treatment	Two international, multi-center, randomized, double-blind, placebo-controlled phase III trials [34]	Bumetanide, placebo	A dose of 0.02 mg/kg BID (oral solution 0.04 mL/kg BID) for patients who weighed	211	107	104	Changes in Social Responsiveness Scale-2(CARS2), Clinical Global Impression Scale, and Vineland Adaptive Behavior Scale	Failed to demonstrate the benefit of bumetanide for the treatment of pediatric ASD.
	A monocenter, double-blind placebo-controlled study [35]	Bumetanide, placebo	0.5mg; 1.0mg; 2.0mg;	72	20; 18; 13	21	Brain imaging	Improved emotional perception
	Double-blind, randomized, and controlled study [36]	Bumetanide, placebo	A dose of 0.5 mg /dose twice a day	80	40	40	CARS	Effective in the treatment of most of the core symptoms of ASD in children with very few side effects. There was an improvement in CARS total score and most of its subscales after 6 months of treatment.

Bumetanide	A randomized, double-blind, placebo-controlled trial [37]	Bumetanide, placebo	0.5mg	119	59	60	CARS, Clinical Global Impressions Scale (CGI) -Global Improvement (CGI-I), Autism Diagnostic Observation Schedule (ADOS), MRS	Safe and effective in improving the core symptoms of ASD. the therapeutic effect of bumetanide on the disease was associated with changes in GABA in the IC,
	A monocenter, parallel-group, patient-randomized, double-blind, placebo-controlled phase-2 superiority trial [38]	Bumetanide, placebo	≤1 mg twice daily	83	42	41	Amsterdam Neuropsychological Task battery (ANT), WISC-III (WISC-III-DS), Wechsler Nonverbal Scale of Ability (WNV-SS), Rey Auditory Verbal Learning Test (RAVLT), and the Rey Visual Design Learning Test (RVDLT)	Putative changes in neurocognitive network organization after treatment, which may imply subtle neurocognitive effects of bumetanide.
	Placebo-controlled double-blind comparison [39]	Oral placebo, whole-plant cannabis extract containing CBD and THC at a 20:1 ratio and pure CBD and pure THC at the same ratio and concentration.	1 mg/kg/d CBD (and 0.05 mg/kg/d THC)	187	93	94	Home situations Questionnaire-ASD (HSQ-ASD) and CGI-Improvement (CGI-I) targeting behavioral problems.	BOL-DP-O-01-W, a whole-plant extract that contains CBD and THC in a 20:1 ratio, improved disruptive behaviors on one of two primary outcome measures and on a secondary outcome, an index of ASD core symptoms, with acceptable adverse events.
Cannabinoid	One double-blind placebo-controlled study [11]	Cannabinoids	The final dose did not exceed 10mg/kg/day (or a total of 400mg/day)	82	41	41	Social Responsiveness Scale, clinical assessment with the Autism Diagnostic Observation Schedule (ADOS), age-appropriate Wechsler test.	Accumulating evidence, mostly from open-label uncontrolled studies, suggests that CBD-rich cannabis may yield benefits for some individuals with ASD. In this study, we demonstrate that this benefit includes improvement in social communication abilities, particularly for participants with high initial severity of core ASD symptoms.
	Randomized, placebo-controlled trial [40]	Cannabinoid placebo	Starting dose was 1mg/kg/dCBD (and 0.05 mg/kg/d THC). The dose was increased by 1mg/kg/d CBD (and0.05mg/kg/d THC) every other day, upto10mg/bodyweight per day CBD (and0.5mg/kg/d THC), for children weighing 20–40kgor7.5mg/kg/d CBD (and 0.375mg/kg/d THC) for weight>40kg (maximum-420mgCBDand21mgTHC per day), divided into 3 daily doses.	100	50	50	Children's Sleep-Habit Questionnaire (CSHQ)	A whole plant extract and a pure cannabinoid preparation, which contained CBD and THC in a 20:1 ratio, did not improve the sleep parameters, as reflected in the CSHQ scores.

Cannabidiol

Cannabis, particularly its non-intoxicating component cannabidiol (CBD), has garnered interest for its potential effects on ASD and associated neurotransmitter pathways. The endocannabinoid system (ECS), which consists of cannabinoid receptors and naturally occurring cannabinoids, plays a vital role in regulating numerous brain functions, including synaptic plasticity and neuromodulation [34]. Research indicates that cannabis oil with a high concentration of CBD may alleviate symptoms such as anxiety, hyperactivity, and sleep disturbances in children diagnosed with ASD. This effect is likely mediated through interactions with the endocannabinoid system, which may enhance the levels of endogenous cannabinoids, such as anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) [35,36,41]. Furthermore, the influence of cannabinoids on serotonin receptors may contribute to improved management of anxiety and mood disorders commonly observed in individuals diagnosed with ASD [37,38,42].

Numerous observational studies have indicated that cannabis extracts containing CBD can result in significant improvements across various symptom domains, including attention deficit/hyperactivity disorder, a range of behavioral disorders, and communication challenges, particularly among individuals exhibiting severe self-injurious behaviors [39]. For instance, a study involving 188 individuals with ASD who received medical cannabis treatment found that a significant proportion reported improvements in symptoms after six months, with 30.1% indicating substantial progress in their condition [8]. Notably, the results were particularly promising among patients without epilepsy, indicating a potentially significant therapeutic benefit of CBD for this population [43]. In addition to alleviating symptoms, the use of cannabis has been associated with improvements in the overall quality of life for both patients and their families. A study involving 20 patients who received full-spectrum cannabis extracts found that 90% reported enhancements in primary and related symptoms, with many participants successfully reducing or discontinuing other medications [38].

While the results seem promising, it is crucial to approach the consideration of cannabis as a treatment option with caution. Research has observed that treatment with cannabis may result in changes in behavior, such as heightened agitation, increased irritability, and reduced appetite [39,44-46]. Individual responses to cannabis can vary considerably, and there is a notable lack of standardized dosing protocols. Caregivers and parents must weigh the potential benefits against the risks and uncertainties associated with cannabis therapy [47]. More about the clinical studies is described in Table 1. Future research, particularly large-scale, well-controlled trials, is needed to fully understand the efficacy and safety profile of CBD in ASD. Additionally, further investigation into the mechanisms underlying their therapeutic effects and potential interactions with other biological systems is warranted.

As cannabis becomes increasingly accepted and legalized in various jurisdictions, disparities may emerge in access to quality cannabis products and treatment options [47]. This situation raises ethical questions regarding fairness and justice in healthcare, especially for marginalized communities [48]. Additionally, the role of healthcare providers in advocating for or against cannabis treatment for ASD presents an ethical dilemma that necessitates careful consideration. This scenario can result in moral distress for clinicians, who may find themselves conflicted between their ethical obligations and the wishes of the families they serve [43]. Figure 3 summarizes the therapeutic efficacy and risks of cannabidiol in treating.

Figure 3: Clinical efficacy and risks of cannabis.

The Potential of Combined Psychopharmacological Therapy

Currently, only two drugs specifically approved by the FDA for the treatment of core symptoms of ASD are aripiprazole and risperidone. These medications are primarily utilized to manage irritability and aggression associated with ASD. However, the symptoms exhibited by individuals with ASD are highly complex and diverse, making a singular pharmacological approach often inadequate to comprehensively address and effectively ameliorate all facets of these symptoms [48]. Given the unique mechanisms of action of various pharmacological agents, combination therapy has emerged as a novel and promising treatment strategy for ASD. For example, the combination of atypical antipsychotics with other medications, such as Selective Serotonin Reuptake Inhibitors (SSRIs), has been investigated to target both core and associated symptoms of ASD. SSRIs are recognized for their potential to alleviate anxiety and depressive symptoms, which are frequently observed in individuals with ASD [49]. Furthermore, the combination of memantine and aripiprazole has been investigated for its potential to manage cognitive deficits and autistic-like behaviors in animal models. This combination therapy has demonstrated improvements in cognitive performance and the restoration of neurotransmitter balance, which is frequently disrupted in individuals with ASD [15]. These findings suggest that targeting multiple pathways through drug combinations may offer a more comprehensive approach to treatment.

It is essential to recognize that combined treatment is not without risk. One drug may enhance or inhibit the metabolism of another, thereby altering the concentration of active drugs in the body and potentially triggering previously unreported adverse reactions. For instance, the concurrent use of antipsychotics with other medications that inhibit cytochrome P450 enzymes can lead to increased plasma concentrations of the antipsychotic, heightening the risk of adverse effects [50]. Consequently, prior to implementing combined treatment, a thorough evaluation of potential drug interactions and risks is imperative, which should include comprehensive in vitro studies and animal experiments. If feasible, small-scale clinical trials should also be conducted.

The Integration of Intervention Training with Pharmacological Approaches

Evidence-based ABA and TEACCH, first-choice ASD treatments, target core symptoms via reinforcement/structure; ABA, individualized, aids early skills with data tracking [51]. For example, Early Intensive Behavioral Intervention (EIBI), a form of ABA, has demonstrated substantial gains in cognitive and social skills [52]. ABA is often considered the first choice for ASD treatment due to its evidence-based effectiveness in addressing core symptoms and promoting long-term skill development [53]. EACCH emphasizes creating a structured, supportive environment tailored to the unique needs of individuals with ASD. TEACCH, on the other hand, uses visual support and predictable routines to help individuals navigate their daily activities independently. This approach is highly effective for individuals who struggle with sensory processing or require a predictable environment to feel secure. Recent studies have shown that TEACCH can improve cognitive and language skills, as well as reduce caregiver stress [54]. However, the effectiveness of TEACCH in autism interventions is still being investigated, with some studies reporting mixed results [55].

Compared to pharmacotherapy, ABA and TEACCH offer several distinct advantages in the treatment of ASD. While medications can provide relief for specific symptoms, they often do not address the core deficits of the disorder. ABA and TEACCH, however, directly target social communication deficits and restricted, repetitive behaviors, leading to long-term improvements in skill development and independence. These behavioral interventions also promote a more favorable psychological and physical foundation for individuals undergoing training, enhancing the overall effectiveness of treatment. Recent research has shown that combining pharmacological approaches with ABA or TEACCH can yield improved outcomes, leveraging the strengths of both interventions to provide comprehensive support [56]. For instance, a feasibility study proposes examining the effects of propranolol, a medication recognized for its efficacy in reducing situational anxiety, in conjunction with EIBI grounded in ABA principles [57]. The rationale behind this approach is that pharmacological agents can potentially target underlying neurobiological mechanisms, thereby enhancing the effectiveness of behavioral therapies. Furthermore, Medications influence the neurotransmitter system, modulating the brain's physiological functions and establishing a more favorable physical and psychological foundation for patients undergoing training. For instance, risperidone alleviates symptoms of irritability, facilitating patient cooperation during intervention training and enhancing the effectiveness of the training [9]. This constructive collaboration between pharmacological and intervention strategies achieves comprehensive rehabilitation support, addressing both physiological and behavioral aspects.

Discussion

Individual Differences in Psychopharmacological Treatments

While risperidone, aripiprazole, bumetanide, and cannabis have all demonstrated varying degrees of efficacy in the medical treatment of ASD, which are illustrated in Table 2, it is crucial to acknowledge the significant differences in individual patient responses to these medications, which are influenced by numerous complicating factors, including gene polymorphisms. Given the heterogeneous nature of ASD, where symptoms and their severity can vary significantly among individuals, a one-size-fits-all approach is frequently inadequate. By customizing combinations of medications and behavioral interventions, clinicians can more effectively address the unique needs of each patient, potentially resulting in improved outcomes in social skills, communication, and overall

quality of life [57, 58]. Factors such as cognitive abilities, age, and initial symptom severity have been identified as predictors of treatment response. For example, children with higher cognitive abilities and lower symptom severity tend to exhibit better outcomes from interventions [59,60]. This suggests that tailoring interventions, regardless of whether they include pharmacological components, could lead to more effective treatment strategies.

Table 2: Mechanism of action, main efficacy, common side effects, indications, and limitations of commonly used drugs in ASD.

Drug Name	Mechanism of Action	Main Efficacy	Common Side Effects	Application Status and Limitations
Risperidone	Blocks 5 - HT2A and D2 receptors	Improves symptoms such as irritability, aggression, and self-harm	Weight gain, drowsiness, extrapyramidal reactions, elevated prolactin levels, and long-term use increase the risk of metabolic syndrome	Long-term clinical application, clear efficacy, but side effects affect long-term use
Aripiprazole	Partial agonist of D2 and 5 - HT1A receptors, antagonist of 5 - HT2A receptors	Reduces hyperactivity, impulsiveness, and stereotyped behaviors, and improves social interaction ability	Headache, insomnia, nausea, vomiting, a few cases of akathisia and anxiety, and a lower incidence of extrapyramidal reactions and elevated prolactin levels than risperidone	Commonly used clinically, with relatively fewer side effects, but still some discomfort symptoms.
Bumetanide	Regulates the chloride ion concentration within neurons and corrects abnormal GABAergic neurotransmission	Improves core symptoms such as social impairment and repetitive and stereotyped behaviors	Mild gastrointestinal discomfort, a few cases of electrolyte disorders, low risk under reasonable doses	The emerging drug has potential, but needs more large-scale clinical trials for verification.
Cannabis	Interacts with the endocannabinoid system and affects neural circuit function	Improves symptoms such as anxiety, sleep disorders, and repetitive and stereotyped behaviors	THC exacerbates psychiatric symptoms, affects cognitive function, long-term use leads to tolerance and dependence, and is restricted by laws	Scarce and controversial research, clinical application is restricted due to psych activity and legal issues.
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Different medications target distinct subgroups of symptoms in patients with autism, necessitating that clinicians accurately select medications based on the specific symptoms presented by the patient. Risperidone and aripiprazole primarily address irritability-related symptoms. Risperidone encompasses various manifestations, including aggression, self-injury, and loss of temper. Aripiprazole is derived from risperidone and is recommended for patients who exhibit intolerance to risperidone or have a poor response, as well as for those with comorbid tic disorders. Cannabidiol primarily targets severe anxiety and sleep disorders, while Bumetanide focuses on social behavior abnormalities and delayed language skills. Different individuals may be more suited to specific medications due to their unique conditions and physical health. In terms of usage restrictions, risperidone and aripiprazole have limitations for patients with certain medical conditions due to the characteristics of the drugs; cannabidiol is constrained by legal and safety considerations, limiting its scope of use; and Bumetanide is still in the research phase, requiring further clarification regarding its applicable population and safety. In practical applications, physicians must comprehensively consider the patient's symptoms, age, physical health, drug safety, and accessibility, weighing the pros and cons to formulate personalized treatment plans (Table 2).

Application of Artificial Intelligence (AI) to Autism Psychopharmacology

The application of Artificial Intelligence (AI) holds significant potential for advancing psychopharmacological interventions for ASD, aligning with the study's focus on evaluating and optimizing pharmacological treatments. A novel predictive framework based on Drug-Target Interaction (DTP) networks has been developed to analyze associations between drugs and their targets, which helps identify potential effective drug combinations for ASD-directly supporting the study's comparison of established and emerging pharmacological agents. Additionally, AI-driven platforms like Panda Omics analyze gene expression profiles from patient samples to identify dysregulated pathways and therapeutic targets, providing

a data-driven basis for understanding the efficacy of drugs such as risperidone, aripiprazole, bumetanide, and cannabidiol evaluated in this review. AI also assists in optimizing combination therapies by analyzing drug-drug interactions and their effects on biological targets, addressing the complexity of ASD symptom heterogeneity that single-agent therapies often fail to resolve. By streamlining drug screening and reducing development time, AI accelerates the translation of promising pharmacological interventions from research to clinical practice, which is crucial for addressing the unmet need for effective ASD treatments highlighted in this study.

Ethical Challenges in The Psychopharmacological Treatment of Autism

Psychopharmacology for ASD raises ethical issues, including regulatory ambiguity, public health impacts, misuse risk, and informed consent challenges, especially for children [20]. The issue of access to treatment also presents ethical dilemmas. The ethical principle of "do no harm" is paramount in medical treatment, and the potential for adverse effects must be weighed against the expected benefits. Clinicians and researchers must ensure that the risks are minimized and that patients are monitored closely during treatment. This raises questions about the adequacy of safety protocols and the responsibility of healthcare providers to protect vulnerable populations, such as children with ASD [33].

The potential for stigmatization associated with the use of antipsychotic medications in children with ASD is another ethical concern. The label of being on a psychiatric medication can lead to social stigma, which may affect the child's self-esteem and social interactions. This stigma can also extend to families, who may feel judged for their child's treatment choices [61]. There is a growing body of evidence suggesting that children from lower socioeconomic backgrounds may have less access to effective treatments for ASD, including pharmacological options like risperidone. This disparity raises questions about equity in healthcare and the ethical obligation to ensure that all children, regardless of their background, have access to appropriate and effective treatment [39].

Conclusion

The current pharmacological management of ASD is multifaceted. Traditional medications like risperidone and aripiprazole are effective in reducing behavioral symptoms, but their side effects can impact patients' quality of life. The emerging drug bumetanide shows promise in treating core symptoms, but further validation through large-scale studies is needed. Cannabis is being explored as a treatment for ASD, but psychoactive risks, legal constraints, and quality control issues limit its clinical use. Overcoming these challenges requires scientific advancements in quality control and safety research, along with collaborative efforts across society. Combination therapies offer potential for ASD treatment, but the complexity of drug interactions necessitates careful evaluation by researchers and clinicians. Precision medicine is crucial in managing ASD, given the variability in individual responses to drug treatment. In-depth studies on pathophysiological mechanisms, along with the integration of artificial intelligence and big data technologies, can lead to the development of more targeted and safer therapeutic agents. Long-term follow-up studies on existing medications will provide valuable insights for clinical practice, benefiting ASD patients and their families by improving their quality of life and integration into society. The seven included double-blind placebo-controlled clinical trials provide foundational evidence for the discussed psychopharmacological interventions, with consistent findings supporting the efficacy of traditional and emerging agents in specific symptom domains of ASD. These studies collectively highlight the need for personalized treatment strategies, as well as further research to validate the long-term safety and effectiveness of these interventions across diverse patient populations.

Ethical Approval and Consent to participate

This study did not involve human or animal subjects, and thus, no ethical approval was required. The study protocol adhered to the guidelines established by the journal.

Human Ethics

No ethical approval was required. The study protocol adhered to the guidelines established by the journal.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Supporting Data

No relevant data was used in the article.

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