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Review

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Pharmacotherapy for the core symptoms of autism spectrum disorder

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Abstract: Autism Spectrum Disorder (ASD) is a range of neurodevelopmental diseases characterized by social dysfunction and stereotypic behaviors. The etiology of ASD remains largely unexplored, resulting in a diverse array of described clinical manifestations and varying degrees of severity. Currently, there are no drugs approved by a supervisory organization that can effectively treat the core symptoms of ASD. Childhood and adolescence are crucial stages for making significant achievements in ASD treatment, necessitating the development of drugs specifically for these periods. Based on the drug targets and mechanisms of action, it can be found that atypical psychotropic medications, anti-inflammatory and antioxidant medications, hormonal medications, ion channel medications, and gastrointestinal medications have shown significant improvement in treating the core symptoms of ASD in both children and adolescents. In addition, comparisons of drugs within the same category regarding efficacy and safety have been made to identify better alternatives and promote drug development. While further evaluation of the effectiveness and safety of these medications is needed, they hold great potential for widespread application in the clinical treatment of the principal symptoms of ASD.

Key words: Autism spectrum disorders; core symptoms; pharmacotherapy; repetitive behaviors; social dysfunction

1 Introduction

Autism spectrum disorder (ASD) is a collective term for neurodevelopmental disorders characterized by social and verbal communication dysfunction, narrow interests, and a lack of flexibility, accompanied by stereotypic behaviors (Lord et al., 2018). ASD is further associated with many non-core symptoms, including anxiety, irritability, aggression, attention deficit and hyperactivity disorder, depression, epilepsy, gastrointestinal and immune function disorders, metabolic abnormalities, and sleep disturbances, among others (Siafis et al., 2022). Epidemiological studies estimate that over 1% of the global population could be diagnosed with ASD, whose prevalence is on the rise. Therefore, ASD has a significant impact on a large number of individuals around the world (Deb et al., 2020).

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ASD patients exhibit distinct phenotypes with varying degrees of severity, while significant individual variability is present. Currently available medicinal treatments cannot be universally applied to all ASD patients, posing challenges for clinical pharmacotherapy and the development of new drugs for ASD (Thom et al., 2021). Despite this diversity, patients share the same core symptoms; therefore, medications developed to target these core symptoms of ASD, which are crucial for enabling individuals to integrate into social life similarly to typical individuals, may be applicable to most patients. Thus, the treatment of core symptoms is the cornerstone of ASD therapy.

Addressing the core symptoms of autism requires identifying the underlying causes and matching them with an appropriate treatment alternative. Meanwhile, the etiology of ASD is likely multifactorial, involving genetic, neurological, immune, and environmental factors, with the environment playing a major role (Lee et al., 2013). Environmental factors include inflammation-related disorders in parents, parental age, perinatal complications, and infections. In addition, xenobiotics, gut microbiota and autoimmunity within the individual's body have also been implicated (Singhi and Malhi, 2023). From a therapeutic perspective, correcting mutations in the genome to treat ASD is challenging, making potential interventions targeting environmental factors more practical (Rylaarsdam and Guemez-Gamboa, 2019). Therefore, the primary treatment approaches for ASD currently focus on medications and behavioral interventions, which are both attractive and feasible strategies.

The core symptoms of ASD typically emerge before the age of three in affected individuals. The brain exhibits its highest degree of plasticity during early childhood, making it more adaptable to environmental stimuli (Kodak and Bergmann, 2020). Consequently, early intervention has the potential to enhance the development of essential social, communicative and cognitive skills in children with ASD. Most infants with ASD can gradually learn to sit, crawl and walk. Thus, it is challenging for parents to recognize delays in social and communication skills during the first year. Additionally, relatively few families undergo ASD-related screenings at birth, and infants are too young to be tested for drug efficacy, limiting research on drugs for this age group. Therefore, childhood and adolescence are considered the optimal periods for pharmacotherapy (Alsayouf et al., 2022). However, there are currently no approved drugs for treating the core symptoms of ASD during childhood and adolescence, highlighting the need and urgency to expand drug development efforts (Hirota and King, 2023). For the above reasons, research on the potential and efficacy of medications for treating the core symptoms of ASD in children and adolescents has become a foremost priority.

2 Objectives

This review aims to systematically examine potential effective medications for treating the core symptoms of ASD in children and adolescents. We analyze the drug mechanism, results of clinical trials, strengths and weaknesses of the drug, and possible misuse of drugs from the standpoint of pharmacology, therapeutic cost, and ease of development. We compare the efficacy and safety of similar medications by identifying potential errors in clinical outcomes and high-

lighting areas for improvement in clinical trials. The primary objective is to advance the quality of clinical trials and help establish standardized medication protocols for future studies. This paper intend to serve as a valuable reference for the development and clinical administration of medications designed to address the core symptoms of ASD.

3 Methods

We conducted a comprehensive search for randomized-controlled-trials and clinical trials in journals and reviews published within the past five years in the databases of Web of Science, EMBASE, MEDLINE, PsycINFO, CNKI, JAMA, Clinicalkey, and PubMed. We used search terms such as “autism spectrum disorder”, “pharmacology”, “treatment”, “core symptoms”, and “medicine”. We focused on the classifications under QV (Pharmacology) and WM (Psychiatry) according to the NIH system. We included all studies conducted on children and adolescents younger than 18 years of age and published from 2019 to 2023 in English language. We excluded gray literature, books, letters to editors, case articles, and conference proceedings. The quality of the included articles was assessed through manual review, including that of the study design, efficacy and safety of the drug, and journal impact factors. The co-primary outcomes of interest were medications for core symptoms (social and verbal communication dysfunction, narrow interest, and lack of flexibility) in children and adolescents. Drugs with significant efficacy were eventually selected for analysis. In this review, we analyzed and summarized existing literature and without performing any human or animal experimentation. Therefore, ethical review or approval was not required.

Approximately 900 studies were identified through the database search. After excluding duplicate studies, we manually screened articles by title and abstract against the inclusion and exclusion criteria, and identified approximately 100 suitable articles. Subsequently, about 60 studies passed the quality assessment and were finalized for full-text examination and analytical discussion.

4 Analysis of medications related to the treatment of autism core symptoms

Statistics show that 59.6% of diagnosed ASD patients have been treated with psychiatric medications such as antipsychotics, ADHD medications, antidepressants, antiepileptic medications, and mood stabilizers (Siafis, et al., 2022). Although there are currently no medications approved by regulatory authorities specifically for treating the core symptoms of ASD (Anagnostou, 2018), some medications have shown significant therapeutic effects on certain core symptoms of ASD in preliminary trials.

4.1 Clinical trial screening results

Through comprehensive review, it has been found that some medications can improve at least one core symptom in children and adolescents with ASD. These medications include

risperidone, aripiprazole, fluoxetine, omega-3 fatty acids, folate, sulforaphane, prednisolone, cannabidiol (CBD), bumetanide, oxytocin, and sequestrant AB-2004 (Panek et al., 2020). The results of the final paper selection are presented in Table 1. The table includes information such as the type and dosage of medication, type of study, number and age of subjects, duration of treatment, measurement tools, and trial outcome.

Table 1 Systematic review of pharmacologic treatments for ASD, summarizing the medications included in selected papers and providing information about clinical trials

Classification	Medication	Doses	Type of study	Subjects	Period of treatment	Outcome measures	Trial outcome
Atypical psychotropic medications	Risperidone (Pandina et al., 2007)	1.37 mg/day	Double-blind, placebo-controlled trial	55 individuals aged 5-12	8 weeks	Aberrant Behavior Checklist-Irritability (ABC-I) subscale	Well tolerated and significantly improved irritability and related aggressive behaviors
	Risperidone or Aripiprazole (Alsayouf et al., 2021)	Risperidone 0.25-2 mg/day Aripiprazole 1-10mg/day	Retrospective case study	10 individuals aged 2 and 4	2 weeks	Childhood Autism Rating Scale 2-Standard Test and Clinical Global Impression scales	Improvement of ameliorating comorbid behaviors
	Fluoxetine (Reddihough et al., 2019)	4 or 8 mg/day-20 or 30 mg/day	Multicenter, randomized, placebo-controlled clinical trial	146 individuals aged 7.5-18	16 weeks	CYBOCS-PDD	Significantly lower scores for obsessive-compulsive behaviors
	Fluoxetine (Herscu et al., 2020)	11.8 mg/day	Randomized controlled trial	158 individuals aged 5-17	14 weeks	Children's Yale-Brown Obsessive Compulsive Scale	No significant improvement were noted on the Children's Yale-Brown Obsessive Compulsive Scale
Antioxidant and anti-inflammatory medications	Omega-3 (Parellada et al., 2017)	962 mg/day and 1155 mg/day for children and adolescents respectively	Multicenter, randomized, double-blind, placebo-controlled, crossover trial	68 individuals aged 5-17	3 weeks	Primary outcome measures were erythrocyte membrane FA composition and TAS. Secondary outcome measures were Social Responsiveness Scale and Clinical Global Impression-Severity.	Significant improvement in Social Motivation and Social Communication subscales scores
	Omega-3 (Doaei et al., 2021)	1000 mg/day	Double-blind, randomized clinical trial	54 individuals aged 5-15	8 weeks	The Gilliam Autism Rating Scale-second edition (GARS-2), food frequency questionnaire (FFQ)	Improvement of stereotyped behaviors and social communication
	Folate (Frye et al., 2018)	2 mg/kg/day-50 mg/day	Double-blind placebo controlled trial	48 individuals aged 7	12 weeks	The Vineland Adaptive Behavior Scale, the Aberrant Behavior Checklist, the Autism Symptom Questionnaire and the Behavioral Assessment System	Improvement of verbal communication
	Folate (Renard et al., 2020)	2 mg/kg/day-50 mg/day	Double-blind, placebo-controlled randomized trial	55 individuals aged 3–10	10 weeks	The aberrant behavior checklist-community (ABC-C)	Significant effect for time × treatment interaction on inappropriate speech, stereotypic behavior, and hyperactivity/noncompliance subscale scores
	Sulforaphane (Bent et al., 2018)	2.5 μmol/day	Randomized controlled trial	15 individuals aged 13-27	12 weeks	Aberrant Behavior Checklist—ABC, Social Responsiveness Scale—SRS	Improvement of behavior and social responsiveness
	Sulforaphane (Zimmerman et al., 2021)	2.2 μmol/kg/day	Randomized parallel double-blind placebo-controlled clinical trial	57 individuals aged 3–12	15 weeks	The Ohio Autism Clinical Impressions Scale (OACIS) The Aberrant Behavior Checklist (ABC)	Improvement of sociability and communication
	Prednisolone (Brito et al., 2021)	1 mg/kg/day	Prospective, double-blind, randomized, placebo-controlled clinical trial	38 individuals aged 3-7	12 months	The Language Development Assessment (ADL) and the Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics (ABFW).	Improvement of language scores
	Prednisolone (Malek et al., 2020)	1 mg/kg/day	Randomized, single-blind, placebo-controlled trial	37 individuals aged 3–12	12 weeks	The Aberrant Behavior Checklist-Community Edition (ABC-C) scale and Childhood Autism Rating Scale (CARS)	Remarkable improvement of core features
	CBD (Hacohen et al., 2022)	2.3 mg/kg/day-3.6 mg/kg/day	Observational study	18 individuals aged 6-7	6–9 months	Clinical assessment and records of patients	The strongest improvements were reported for Seizures, Attention Deficit/Hyperactivity Disorder, Sleep Disorders, and Communication and Social Interaction Deficits
	CBD (Fleury-Teixeira et al., 2019)	3.75 mg/kg/day-6.45 mg/kg/day	Observational study	188 individuals aged 5-18	6 months	Subjective self-report of the patient's parent's observation	Seemingly effective option to relieve symptoms, mainly: seizures, tics, depression, restlessness and rage attacks
Ion channel medications	Bumetanide (Sprengers et al., 2021)	1 mg/day	Proof of concept pilot study	9 individuals aged 16-26	10 months	Fmri, Eye-tracking	Improvement of specific aspects of social processing in autism
	Bumetanide (Zhang et al., 2020)	1 mg /day	Pilot study	10 individuals aged 3-6	3 months	Primary [Children Autism Rating Scale (CARS)], secondary [Clinical Global Impressions (CGI)], and exploratory [inhibitory (γ-aminobutyric acid, GABA) and excitatory (glutamate, Glx) neurotransmitter concentrations measured in the insular cortex (IC) and visual cortex (VC) by magnetic resonance spectroscopy (MRS)]	Improvement of repetitive behaviors and stereotypic impressions
	Bumetanide (Lemonnier et al., 2017)	0.5, 1.0 or 2.0 mg twice/day	Multicenter phase 2B study	88 individuals aged 2-18	3 months	The Childhood Autism Rating Scale (CARS), the Social Responsive Scale (SRS) and the Clinical Global Impressions (CGI) Improvement scale (CGI-I)	Improvement of social interaction behaviors and restricted interests as well as repetitive behaviors
Hormonal medications	Oxytocin (Le et al., 2022)	a standard 24 IU dose/day	Pilot double-blind, randomized, crossover design trial	41 individuals aged 3-8	6 weeks	Autism Diagnostic Observation Schedule-2 (ADOS-2) and social responsivity scale-2 (SRS-2). Secondary measures included cognitive, autism- and caregiver-related questionnaires, and social attention assessed using eye-tracking	Positive social interactions can improve improvement of social communication, restricted, and repetitive behaviors
	Oxytocin (Parker et al., 2017)	a standard 24 IU dose twice/day	Double-blind, randomized, placebo-controlled, parallel trial	32 individuals aged 6-12	4 weeks	The Social Responsiveness Scale (SRS)	Enhances social abilities
	Oxytocin (Sikich et al., 2021)	a standard 24 IU dose twice/day	Placebo-controlled phase 2 trial	41 individuals aged 3-17	24 weeks	The ABC modified Social Withdrawal subscale (ABC-mSW)	No significant between-group differences in the least-squares mean change from baseline on measures of social or cognitive functioning
Gastrointestinal medications	Sequestrant AB-2004 (Stewart Campbell et al., 2022)	500 to 6000mg/day	Open-label, single-cohort, multiple-ascending-dose clinical trial	30 individuals aged 12-17	8 weeks	The Pediatric Anxiety Rating Scale (PARS), the Aberrant Behavior Checklist (ABC), the Social Responsiveness Scale (SRS-2), the Repetitive Behavior Scale Revised (RBS-R) and the Vineland Adaptive Behavior Score (VABS-3), the 6-GSI, the Bristol Stool Scale (BSS) and the Gastrointestinal Symptom Rating Scale (GSRS)	Reduced levels of gut microbial metabolites, improvements in irritability and anxiety largely

4.2 Classification of medications used to treat autism

In this review, existing medications for ASD are systematically categorized based on their drug targets and mechanisms of action. The involved groups include atypical psychotropic medications, antioxidant and anti-inflammatory medications, and other medications. the first two of the above have a well-established history in clinical application, supported by substantial clinical evidence. On the other hand, recent advancements have identified novel medications targeting potential sources of ASD. Some of these novel agents have shown good efficacy in improving the core symptoms of autism. For example, AB-2004 addresses gastrointestinal concerns, bumetanide modulates ion channels to influence γ-aminobutyric acid (GABA) activity in neurons, and oxytocin regulates hormone levels. These three categories of medications primarily focus on distinct biological mechanisms implicated in the onset of ASD, addressing the various etiological factors. The initial group primarily targets dysfunction in two neurotransmitters: dopamine and serotonin, while the second group targets oxidative stress and neuroinflammatory responses, and the third group consists of classic but repurposed medications. Initially developed for the treatment of other disorders, these medications have been identified as potentially associated with multiple ASD etiological hypotheses. These include the excitatory-inhibitory imbalance of glutamate and GABA (Siegel-Ramsay et al., 2021), the gut-brain-axis hypothesis (Srikantha and Mohajeri, 2019), and abnormalities in brain structure and function (Ecker et al., 2015). These drugs are expected to provide suitable, safe and effective interventions for children and adolescents with ASD and are likely to be widely used in clinical practice.

The above categorization facilitates a clear understanding of the specific ASD triggers that these medications potentially target, contributing significant evidence to the understanding of the underlying causes of ASD. Moreover, it allows for the comparison of efficacy and safety among drugs within the same category, with the aim of identifying improved alternatives and advancing drug development; it also provides a basis for the comprehensive evaluation of the advantages and disadvantages inherent to different medication categories. It can be discerned that certain medications have a pronounced impact on specific autism-related complications, potentially opening the path for tailored multi-drug combinations that align with individual patient symptoms.

4.3 Atypical psychotropic medications

Risperidone and aripiprazole are atypical psychotic medications acting as dopamine and serotonin receptor antagonists in the treatment of ASD (Lord, et al., 2018). Compared to typical psychotropic medications like methylphenidate and haloperidol, atypical psychotropic medications are more potent and cause fewer side effects (Scala et al., 2023). Risperidone and aripiprazole are the only medications approved by the United States Food and Drug Administration (FDA) specifically for use in ASD children aged 5 to 16 years (Alsayouf, et al., 2022). Over time, they have become standard medications for managing irritability and related aggressive behaviors in ASD patients (Kompella et al., 2022). In a Canadian study, it was found that risperidone significantly reduced children's irritable behaviors by more than 50% and also mitigated their hyperactivity (Pandina et al., 2007). Similarly, a study in Dubai revealed that after taking risperidone and aripiprazole, all children with ASD showed improvements in their core symptoms, and 60% of patients exhibited a complete remission of their symptoms associated with ASD (Alsayouf et

al., 2021). However, despite their effectiveness in alleviating the core symptoms of ASD, these medications can lead to various physiological adverse reactions, such as weight gain, hyperprolactinemia, mild sedation, heart symptoms, and metabolic disorders (Anagnostou, 2018; Cicala et al., 2020), which can significantly impact the normal growth, development and daily life of children.

While both risperidone and aripiprazole provide some improvement in social dysfunction and repetitive behaviors, the long-term and high-dose application of these medications can lead to the above significant side effects. Nonetheless, the side effects and therapeutic effects may vary from person to person; hence, close monitoring and regular follow-up of drug users are necessary. Currently, clinicians rely solely on their individual clinical experience to determine the dosage, which may result in the risk of overprescribing and overuse of these medications. This is due to the lack of accurate dosage determination methods based on patients' physical characteristics and the severity of the condition. Given that no other approved medications are available for treating ASD, there is an urgent need to develop stricter guidelines for these two medications, as well as safer and more effective drugs that target the core symptoms of ASD.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has demonstrated substantial efficacy in alleviating obsessive-compulsive disorder (Wu and Qin, 2023). A clinical trial conducted in Australia found that fluoxetine significantly reduced obsessive-compulsive behaviors in children with ASD (Reddihough et al., 2019). However, a different trial reported no significant change in the repetitive behaviors of children and adolescents with ASD after taking fluoxetine (Herscu et al., 2020). These differences in experimental outcomes may be attributed to dosage variations, with low doses not achieving sufficient effects. On the other hand, increasing the dosage and extending the treatment period might yield remarkable therapeutic effects on repetitive behaviors in ASD patients. The most common adverse reactions reported by fluoxetine users include insomnia, respiratory infections, diarrhea, and vomiting. Overall, this drug is considered relatively safe and well-tolerated (Hetrick et al., 2021). Nevertheless, there is a scarcity of trials investigating the use of fluoxetine to alleviate the core symptoms of ASD, and collecting further clinical evidence is necessary by including larger and more diverse participant groups.

4.4 Anti-inflammatory and antioxidant medications

Omega-3 has been found to have neuroprotective, anti-inflammatory and antioxidant effects (Arab et al., 2006). These essential fatty acids cannot be synthesized in the body and must be obtained through nutrition for normal brain growth and function. Inadequate brain development has been linked to an imbalance in the ratio of omega-6 to omega-3 in cell membranes (Luchtman and Song, 2013). A study conducted in New Zealand found significant improvements in social motivation and communication in children who took omega-3 supplements (Parellada et al., 2017). Another clinical trial demonstrated that omega-3 treatment reduced repetitive behaviors and improved social interaction in children (Doaei et al., 2021).

Folate, a water-soluble B vitamin, has shown anti-inflammatory and antioxidant effects (Vahabzadeh and Mcdougle, 2013), and disruptions in folate-related metabolism have been associated with abnormal glutathione levels in relation to ASD (Frye and James, 2014). Supplementation with folate during pregnancy can potentially reduce the risk of ASD in the fetus (Surén

et al., 2013). Up to 23% of ASD children have abnormally low cerebrospinal fluid folate levels. Clinical trials conducted in the United States have provided evidence of the beneficial effects of high-dose folate treatment on verbal communication in individuals with ASD (Frye et al., 2018). Similarly, a clinical trial in Iran investigated the use of folate as an adjunct to risperidone and observed a significant reduction in inappropriate verbal and repetitive behaviors in children with ASD (Batebi et al., 2021). Moreover, a trial conducted in France demonstrated that high-dose folate contributed to significant improvements in verbal communication and social interaction among children with ASD (Renard et al., 2020).

Sulforaphane, a common antioxidant found in vegetables, has been identified as an anti-cancer bioactive substance. Furthermore, its anti-inflammatory and antioxidant properties may contribute to the improvement of ASD (Momtazmanesh et al., 2020). The onset of ASD has also been associated with physiological abnormalities outside the central nervous system, such as immune dysregulation (Ashwood et al., 2011), inflammation (Dantzer et al., 2008), reduced antioxidant capacity, elevated oxidative stress levels (James et al., 2006; Ashwood, et al., 2011), and mitochondrial dysfunction (Rossignol and Frye, 2012). A study in the United States reported significant improvement in abnormal behavior and social dysfunction in children with ASD after sulforaphane treatment (Bent et al., 2018). Another clinical trial also found significant improvements in abnormal behavior in children (Zimmerman et al., 2021). In a clinical trial using sulforaphane as an adjunct to risperidone, the drug showed significant effects in alleviating irritability and hyperactivity symptoms in children with ASD, while no significant improvements were demonstrated in stereotypic behavior and inappropriate speech (Momtazmanesh, et al., 2020). This drug has mild side effects, including insomnia, headache, restlessness, and diarrhea. However, the trial duration was short and the sample size was small, lacking robustness in demonstrating the drug's significant therapeutic effect on ASD (Lee et al., 2021). Oxidative stress has been considered as a potential mechanism involved in the onset of ASD, particularly during the early developmental stages. It has been suggested that antioxidant medications should be administered during early childhood as their effectiveness might diminish with patient age, making them more suitable as supplementary treatments. However, it is worth noting that the diagnosis of ASD in young children heavily relies on caregiver assessments, and improvements in ASD-related behaviors observed in toddlers may be attributed to physiological growth rather than solely to the use of supplements. While many experiments highlight the role of dietary supplements as adjunct therapies, there is currently insufficient robust evidence to confirm the singular efficacy of dietary supplements in treating ASD. Therefore, more multicenter clinical trials are needed that involve a broader range of ASD populations to further validate the effectiveness of these supplements and test their applicability for patients from different age groups.

Dietary supplements such as omega-3, folate and sulforaphane have been shown to have minimal side effects when appropriately dosed for children. These supplements can be obtained through regular dietary intake, and they are affordable. High-quality omega-3, folate and sulforaphane products and medications are readily available in the international market. Although the exact improvement in the core symptoms of ASD in response to dietary supplements is not yet clear, it is important to recognize that the therapeutic effects of medications are often difficult to precisely establish, and improvements observed in a patient's condition may be the result of a

combination of various dietary factors. Therefore, when considering the daily dietary intake, it becomes challenging to exercise accurate control over medication dosage. This necessitates further research into determining the optimal dosage and duration of dietary supplements for ASD treatment.

Prednisolone is a corticosteroid primarily used to treat neuroinflammation and autoimmune diseases (Duffy et al., 2014), which in turn are linked to ASD (Tye et al., 2018). A clinical trial in Brazil showed that prednisolone significantly improved language skills in children with ASD (Brito et al., 2021). Another trial in Iran demonstrated that prednisolone, as an adjunct to risperidone, significantly improved hyperactivity, sleepiness, stereotypic behaviors, and inappropriate speech in children with ASD (Malek et al., 2020). Prednisolone therapy is generally associated with only mild side effects such as moderate hypoglycemia and low blood pressure. However, as an anti-inflammatory medication, further experimental research is needed to elucidate the therapeutic mechanisms of prednisolone in ASD. To establish appropriate usage standards, it is crucial to increase the sample size and extend the follow-up periods in clinical trials involving prednisolone as an adjunct or standalone treatment for ASD. Many trials targeting children have utilized low doses of prednisolone, potentially limiting its efficacy in ASD treatment. Therefore, exploring higher dosages of prednisolone is necessary to better evaluate its effects on ASD patients and determine the optimal therapeutic dosage.

Cannabidiol, a non-toxic component of the cannabis plant, has shown promise in treating a range of neuro-psychiatric disorders and is now recognized as a potential anti-inflammatory and antioxidant medication (Wang et al., 2022). Several studies have indicated that CBD possesses analgesic, neuroprotective and anti-inflammatory properties, as well as the ability to reduce oxidative stress (Vallée et al., 2021). Cannabis contains over 100 phytocannabinoids, including delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient, and CBD, which has anxiolytic, antipsychotic and anticonvulsant effects and is non-toxic (Pedrazzi et al., 2022). CBD belongs to a group of terpenophenolic compounds found in cannabis and the nervous and immune systems of animals. These compounds have analgesic and anti-asthmatic effects and are used extensively to treat neurological and psychiatric disorders such as Parkinson’s disease and Alzheimer’s disease (Whiting et al., 2015).

Endocannabinoids participate in various neural regulatory activities, impacting cognitive function, emotional regulation, social motivation, reward processing, and other behavioral indicators (Mechoulam and Parker, 2013). Animal models of ASD suggest that dysregulation of the endocannabinoid system may contribute to behavioral abnormalities (Wei et al., 2015). In addition, serum samples from children with ASD have been found to have lower levels of endocannabinoids compared to typically developing children (Aran et al., 2019b). A study conducted in Israel demonstrated that treatment with CBD-rich cannabis significantly improved social communication issues in children with ASD (Hacohen et al., 2022). Similarly, a study conducted in Brazil showed that CBD improved motor development, communication, social interaction, and cognitive performance in children with ASD (Fleury-Teixeira et al., 2019).

The main adverse reactions associated with cannabinoid use include sleep disturbances, irritability and reduced appetite (Bar-Lev Schleider et al., 2019). While recreational cannabis use can lead to addiction, cognitive impairment and schizophrenia, especially in some countries that

have legalized it, these complications are primarily associated with THC (Pintori et al., 2023). On the other hand, CBD is a natural substance with significantly lower toxicity and no psychoactivity, which helps maintain endocannabinoid levels at a reasonable range, allowing patients to feel physically well without the addictive effects of THC (Aran et al., 2019a). However, there is still limited data on the safety and tolerability of cannabinoids in adolescents and children. Further clinical investigation is needed to determine the appropriate dosages of CBD for different ages and types of patients with ASD. Furthermore, extensive randomized double-blind clinical trials involving a larger number of ASD patients are required to determine the actual therapeutic effects of CBD on improving the core symptoms of ASD. However, due to strict cannabis regulations in many countries, increased safety and favorable evidence is needed to conduct large-scale clinical trials, which hinders further research on this class of drugs.

4.5 Other medications

4.5.1 Ion channel medications

Bumetanide, a potent diuretic drug utilized in pediatric clinics, has been found to lower neuronal chloride levels and facilitate the transition of GABA from an excitatory to an inhibitory state (Hadjikhani et al., 2015; Sprengers et al., 2021). It is believed that ASD is caused by an unsuccessful shift in GABA activity in neurons from excitatory to inhibitory (Lozovaya et al., 2019). Bumetanide can augment the effects of GABA and maintain the balance between excitatory and inhibitory signals in the brains of individuals with ASD (Hadjikhani, et al., 2015). Previous studies conducted on animals and small clinical trials have validated the efficacy of bumetanide, an established drug, in ameliorating core symptoms associated with ASD. For instance, a study conducted in the Netherlands revealed that bumetanide alleviated repetitive behaviors in children with ASD (Sprengers, et al., 2021). Similarly, it was experimentally demonstrated that the administration of bumetanide significantly ameliorated repetitive behaviors and stereotypic behaviors in children with ASD (Zhang et al., 2020). A study conducted in France also indicated that bumetanide ameliorated social interaction behaviors, narrow interests and repetitive behaviors in children and adolescents (Lemonnier et al., 2017).

However, reaching effective concentrations of bumetanide in the blood is challenging. Besides, it may also have limited penetration into the brain due to incomplete crossing of the blood-brain barrier. As a result, the therapeutic efficacy of bumetanide in ASD may be constrained. Researchers are currently investigating and developing more effective strategies to enhance the brain penetration of bumetanide and optimize its efficacy for the treatment of ASD (Hadjikhani, et al., 2015). Furthermore, it remains uncertain whether bumetanide can fully restore the impaired GABA switch in individuals with ASD. Notably, the significant adverse reactions associated with bumetanide primarily comprise diuretic effects and hypokalemia (Sprengers, et al., 2021). Nevertheless, these are minimal under chronic conditions and can be managed through additional potassium supplementation (Lemonnier et al., 2012). Consequently, despite its limited brain penetration, we posit bumetanide exhibits promising prospects as a safe and effective treatment for reducing the severity of ASD due to its effects of alleviating social dysfunction and enhancing activity levels. Consequently, this drug presents a viable alternative therapeutic approach for adolescents with ASD and holds promise as a novel medication for effectively treating

younger children with ASD. However, in the future, it is crucial to implement stringent criteria to identify suitable candidates for this medication to mitigate potential unknown side effects.

4.5.2 Hormonal medications

Oxytocin, a pituitary neuropeptide, plays a regulatory role in human emotions and impacts social and cognitive functions (Cai et al., 2018). As opposed to other methods, intranasal administration of oxytocin possesses the ability to penetrate the blood-brain barrier, enhance drug bioavailability, and expedite drug effects (Panek, et al., 2020). A study conducted in China demonstrated that oxytocin treatment significantly improved social communication, as well as reduced restricted and repetitive behaviors in children with ASD (Le et al., 2022). Additionally, another trial assessing the application of intranasal oxytocin in children with ASD reported a noteworthy improvement in their social abilities (Parker et al., 2017). In contrast, a 24-week trial conducted with children and adolescents diagnosed with ASD found no significant changes in social interaction or cognitive function indicators among the participants (Sikich et al., 2021). This particular study differed from previous clinical trials in that it administered oxytocin by a flexible dosing strategy based on adverse responses rather than weight changes. The adverse reactions reported by the participants were not significant, although the results could be influenced by various factors, including potential undetected adverse reactions. Furthermore, the experimental design was complex, potentially influenced by additional confounding factors. Therefore, caution should be exercised when generalizing the experimental conclusions.

The most common adverse reactions observed for intranasal oxytocin are nasal discomfort and skin irritation. However, considering a larger number of participants, the adverse reactions become insignificant, indicating that intranasal oxytocin is well-tolerated and safe to use in the ASD population (Cai, et al., 2018). Importantly though, oxytocin may impact physiological functions in female participants, such as the menstrual cycle and fertility (Bethlehem et al., 2017). As such, the inclusion of female participants in oxytocin studies has been limited, necessitating further research to broaden their representation. We have observed that intranasal oxytocin can cause discomfort in participants. Children and adolescents may be more sensitive than adults and may struggle with adherence to the treatment regimen, potentially leading to issues with inadequate dosing. This could explain the difference in the efficacy of oxytocin treatment between adults and children. Future clinical research must have a greater scope of gender and age groups to more precisely determine the side effects and optimal dosages of oxytocin for various ASD patient profiles. The absorption mechanism of oxytocin and the duration of its effects are still unclear. Thus, the mode of administration and time intervals between doses may affect the reliability of experimental results. In future intervention trials, it will be beneficial to explore more convenient and effective administration methods of oxytocin specifically designed for children. More precise details regarding the time intervals between doses and the duration of medication efficacy should also be clarified.

4.5.3 Gastrointestinal medications

Sequestrant AB-2004, also known as AST-120 (Niwa et al., 1991), is a gastrointestinal-restricted adsorbent. Unlike some other substances, it is not broken down by digestive fluids

or bacteria. When orally administered, AB-2004 binds aromatic or phenolic metabolites in the intestine, preventing their absorption by the gastrointestinal tract and facilitating their excretion (Huang et al., 2021). Gastrointestinal (GI) issues, such as constipation, diarrhea and inflammatory bowel disease, are commonplace in individuals with ASD. These GI issues have the potential to impact endocrine, immune and metabolic functions as GI microbiota and their metabolites can enter the bloodstream. Through the gut-brain-axis, these factors may contribute to abnormal neurological development and potentially exacerbate ASD symptoms (Yang et al., 2018). A recent study indicated that oral administration of AB-2004 can influence GI microbiota metabolites and improve social dysfunction and repetitive behaviors in adolescents diagnosed with ASD (Stewart Campbell et al., 2022).

Nearly half of children with ASD experience one or more chronic gastrointestinal disorders (Zebrowska et al., 2021). Unfortunately, due to the limited communication abilities of these children, GI issues often go unnoticed by healthcare professionals. This can impede treatment and worsen the underlying conditions (Martinez-Gonzalez and Andreo-Martinez, 2019). To address this problem, future double-blind, placebo-controlled trials are needed, especially in the absence of a control drug. It is also worth noting that the phase 1b/2a clinical trial only involved a small group of adolescent ASD participants. To gain a thorough understanding of the effects of AB-2004, it will be essential to conduct phase 2b and phase 3 clinical trials. The specific mechanism by which AB-2004 alters brain connectivity remains unclear. One hypothesis suggests that AB-2004 may improve gut health by adsorbing aromatic or phenolic metabolites, subsequently influencing brain areas associated with ASD. Another possibility is that the drug directly affects the nervous system by crossing the blood-brain barrier, thereby improving ASD symptoms.

Thus far, researchers have not been able to elucidate the specific links between the impact of AB-2004 on gut microbiota metabolites and the blood system, endocrine system and nervous system. It also needs further investigation how AB-2004 influences brain functional connectivity and behavioral regulation. Understanding the mechanism of action regarding changes in brain functional connectivity and behavior would be crucial. We propose that AB-2004, which can be administered orally at a specific dosage, is a cost-effective option with low compliance requirements. The precise causal relationship between GI symptoms and ASD remains unclear. It is plausible that different types and severities of ASD are correlated with distinct gut microbiota compositions. Therefore, even though AB-2004 may adsorb gut aromatic or phenolic metabolites, it may not be suitable for all individuals with ASD. Consequently, further research is necessary to identify the specific ASD subtypes that can benefit from AB-2004 treatment.

5 Discussion

Among the various drugs used for the treatment of ASD, atypical psychotropic medications are the most commonly employed ones due to their comprehensive modulation of multiple receptors in the central nervous system. However, the specific effects of dopamine and serotonin in individuals with ASD remain poorly understood. Attempting to explain the pathogenesis of ASD solely based on the complete inhibition or enhancement of dopamine and serotonin activity

oversimplifies the related mechanism and lacks specificity. Individuals exhibit varying responses to medications, with a range of side effects and potential allergies, which may hamper the feasibility of extensive and prolonged treatment. Therefore, medication criteria must be continuously adjusted based on individual differences and therapeutic outcomes. While fluoxetine is primarily used for depression and obsessive-compulsive disorder, it has also shown efficacy in treating obsessive-compulsive behaviors in ASD. However, further exploration is required to determine the mechanism underlying the alleviation of other core symptoms of ASD. Prednisolone, as an anti-inflammatory and antioxidant medication, is primarily prescribed for allergic and auto-immune inflammatory diseases. However, its potential side effects are more pronounced under high doses over a prolonged period, necessitating the exercise of caution for application in children, who should also avoid long-term use. Despite the limited research involving children and adolescents, it is imperative to broaden investigations on prednisolone, especially regarding its impact on repetitive and stereotypic behaviors. The potential side effects of this drug are particularly important to consider, as they could hinder growth and development and potentially cause enduring harm to young individuals. Therefore, rigorous safety assessments and further testing in this age group are mandatory.

Sulforaphane, folate and omega-3 are antioxidants with anti-inflammatory properties and the ability to reduce oxidative stress in ASD. However, it remains unclear whether oxidative stress in the brain is the cause or a consequence of ASD. If the latter, the therapeutic effect of these drugs may be limited. Nevertheless, the findings of the present review indicate that antioxidant supplementation may hold promise as a treatment option for ASD. Sulforaphane, folate and omega-3 are three dietary supplements with good clinical safety profiles. They are easily obtainable through everyday foods such as natural fruits, vegetables and animal offal. They are also cost-effective and, when transformed into medications, tend to have minimal side effects. According to some studies, these medications have proven effective as adjuncts to atypical psychiatric medications. Unlike cannabinoids as the only psychoactive medication mentioned in this review, CBD is a medicinal compound that lacks psychoactive properties. The traditional uses of medicinal cannabis, particularly CBD, are primarily for sedation and pain relief. While CBD has not been extensively studied in the field of ASD, the unique nature of CBD and the strict regulations surrounding it in some countries regarding cultivation and research present limitations to research progress on CBD in ASD therapy.

A number of medications, originally intended for other conditions, have shown significant efficacy in treating autism. Recent research has revealed their effectiveness in ameliorating the core symptoms of autism. Oxytocin, for instance, is most effective when administered through nasal spray for the treatment of ASD. However, unlike other medications, pediatric ASD patients require adult supervision and assistance to ensure proper adherence to the prescribed dosage. Trials of oxytocin on ASD patients of various ages and genders have been incomplete, warranting more comprehensive investigations to include different types of ASD groups, in order to draw more generalizable conclusions. AB-2004, a small molecule sequestrant acting as a gastrointestinal adsorbent, has demonstrated a favorable clinical safety and tolerability profile. It improves gastrointestinal and ASD-related symptoms by adsorbing intestinal aromatic or phenolic metabolites. Bumetanide, previously used for edema treatment, has low toxicity but has dietary con-

traindications. Recent findings suggest its potential in alleviating the core symptoms of ASD, offering hope for younger children with limited access to rehabilitation resources. However, the drug is still in the research stage, and further progress is required before it can be applied in clinical settings and become widely available. In addition, continuous adjustments to medication standards based on individual differences and treatment duration are essential.

Clinical trials evaluating the efficacy of drugs in treating the core symptoms of ASD commonly employ scales. However, these scales vary among studies, leading to disparate results for the same drug. Therefore, multiple measures and experimental designs should be applied to validate the effectiveness of a drug before its clinical implementation. Furthermore, research on drug treatments for ASD is region-specific, with a limited inclusion of patients of all ages and genders from various parts of the world. Consequently, even if a drug yields statistically significant results, its applicability may not be extended universally, necessitating adaptation to different geographic regions.

In this comprehensive comparative analysis, we focus on medications for core symptoms of ASD in children and adolescents. In contrast to previous overviews, our evaluation encompasses the aspects of safety, tolerability and efficacy of each drug. This systematic approach is crucial to providing a more nuanced array of treatment options tailored to the diverse manifestations of ASD. We emphasize the significance of rigorous testing during the clinical phases to facilitate the integration of drugs into clinical use. To this end, current medications targeting the core symptoms of ASD demonstrate deficiencies in research methodologies and application scenarios. Most critically, there is a lack of robust guidelines governing their use. Therefore, we offer guidance and insights into the development and testing of medications for children and adolescents with ASD, with a focus on drug treatments. Nevertheless, we refrain from providing specific methodologies; instead, we emphasize future prospects for the development and testing of pharmaceutical interventions. At present, there is no international consensus on the pharmacological treatment of the core symptoms of ASD. Drug interventions have the advantage of targeting core symptoms specifically, addressing the underlying causes more directly and providing more immediate solutions than other therapies. However, it is essential to acknowledge that the combination of different therapies is imperative in the successful treatment process for ASD, particularly in addressing the social functional impairments experienced by affected individuals. Previous research suggests that pursuing drug treatment according to various approaches may yield more significant results. Nevertheless, specific and widely applicable effective treatment protocols remain to be developed, necessitating further exploration in this field.

Data Availability Statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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Author Contributions

Peiying Tan and Hongyan Geng designed this review framework; Peiying Tan, Hongyan Geng, Lizhang Zeng, and Hongyan Geng wrote the original draft; Xiaolin Shen refined the manuscript; Lizhang Zeng, Xuchu Weng, and Hongyan Geng provided supervision and guidance. All authors have read and approved the final manuscript.

Conflict of Interests

All authors declare no conflict of interests.

Ethics guidelines

This article does not contain any studies with human or animal subjects performed by any of the authors.

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