

Pharmacological approaches in the treatment of autism: a narrative review

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Received on: Jul 29, 2021. Accepted on: Aug 31, 2022. Available online: Sep 5, 2022.

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in communication and social interaction and by the presence of repetitive and restricted behaviors. To review the literature on drug interventions in the treatment of ASD in children and adolescents. Narrative review conducted at a university in São Paulo, Brazil. Search of the literature of studies published from 2005 to 2022, in Portuguese, English and Spanish, in the SciELO, PubMed, SCOPUS, LILACS and TripDatabase databases. Risperidone alone improved stereotyped patterns of behavior. Associations with aripiprazole or galantamine reduced irritability and managing the behavioral symptoms, respectively. Ginkgo biloba, associated to risperidone, led to an improvement in the Aberrant Behavior Checklist-Community (ABC-C) subscales scores. The association with sulforaphane exhibited a greater improvement in irritability and hyperactivity/noncompliance scores. Omega-3s reduced gesture use and hyperactivity. Bumetanide reduced restricted interests and repetitive behavior compared to placebo. Intranasal oxytocin improved social skills. The AB-2004 showed improvement in behavioral endpoints, especially anxiety and irritability. Folinic acid improved verbal communication in non-syndromic ASD children. Prednisolone increased language scores. There is not a drug that treats all of them and the possibility of significant adverse effects must be adjusted according to the symptoms and clinical response.

Keywords: Autism spectrum disorder; Akinetic mutism; Rett syndrome; Asperger syndrome.

Introduction

Autism spectrum disorders (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors [1]. These symptoms form the core of the disorder, but the severity of their presentation varies. It is a pervasive and permanent disorder, with no cure, although early intervention can change the prognosis. ASD covers autistic disorder, Rett Syndrome, Asperger's Disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified [2].

People with autism have difficulty in establishing normal conversations, whether involving verbal or non-verbal aspects and demonstration of social interest, emotion, and affection; difficulty in establishing relationships, interests, and activities; insistence on the same things; stereotyped movements; uncompromising adherence to a routine; and hyper- or hypo-reaction to sensory stimuli, including food selectivity [2].

The prevalence of autism has increased in the United States from 1 for every 150 children aged 8 years in 2000-2002, to 1 for every 58 in 2014. This increase is related to the expansion of diagnostic criteria with adequate psychometric properties and the

development of tracking instruments [1].

Due to brain plasticity, the gold standard treatment for ASD is early intervention, which should start as soon as there is suspicion or immediately after diagnosis by an interdisciplinary team, being essential for the improvement of the clinical picture of autism, generating significant gains and lasting in the child's development [3]. The intervention consists of a set of therapeutic modalities that aim to increase the child's potential for social development and communication, protect intellectual functioning by reducing damage, improving quality of life, and directing skills towards autonomy [1].

There is no medication that treats all symptoms of autism, but many children use drugs to alleviate repetitive behaviors, stereotypies, inattention, irritability, hyperactivity, impulsivity, and sleep disorders. This allows the child a greater focus and tranquility in the tasks they want to perform. Risperidone and Aripiprazole have been widely studied and approved by the FDA (Food and Drug Administration), the agency responsible for the control of foods and medicines in the United States) to be used in children over 5 years old with difficulties caused by autistic traits [4].

This study proposes to assess the possible therapeutic bases for the

different spectrums of autistic disorder through a narrative review.

Methods

We conducted a review of the literature considering the period from January 1, 2005, to March 2022. We used the MEDLINE database (via PubMed) and LILACS (via Virtual Health Library) to identify relevant articles on the autism spectrum disorders, without restrictions on languages. Different combinations of keywords and MeSH terms were used as search strategies to ensure a broad search strategy: *"autism spectrum disorders"*, *"akinetik mutism"*, *"asperger syndrome"* and *"autistic disorder"*.

The titles and abstracts of citations identified through these search strategies were screened for eligibility. The details of the search strategy are shown in Table 1.

The structured research was considered using the PICO (Patient, Intervention, Comparison and Outcome) strategy (Chart 1). The focus of this research was randomized clinical trials and we defined the following inclusion criteria: (1) individuals aged between zero and 19 years diagnosed with ASD (including autism, Asperger's Syndrome or pervasive developmental disorder, not otherwise specified); (2) publication vehicle: journals with strict editorial criteria for publication and peer review; (3) the dependent variable needs to be associated with behavioral symptoms of ASD and/or involved therapies; (4) original research studies with a high level of detail on methods and results; (5) language of publication: articles published in full in Portuguese, English or Spanish; (6) time of publication: articles published in full during the last 20 years.

Chart 1. Acronym for the population, intervention, comparison, and outcome method.

Population: Children and Adolescents with ASD

Intervention: Therapeutics in different spectrum

Comparison: No treatments, conventional therapies, and other behavioral treatments

Outcome: Changes in symptoms of individuals with ASD

Study Type: Randomized Controlled Clinical Trials

Table 1. Details of the search strategy.

Database	Search strategies	Papers found
MEDLINE (PubMed)	#1 – (“autism spectrum disorders”) AND (“akinetik mutism”) AND (“asperger syndrome”)	68
	AND (“autistic disorder”)	32
	#2 – (“autism spectrum disorders”[Mesh Terms]) AND (“autistic disorder”[Mesh Terms])	
LILACS (BVS)	#1 – (“autism spectrum disorders”) AND (“akinetik mutism”) AND (“asperger syndrome”)	24
	AND (“autistic disorder”)	5
	#2 – (“autism spectrum disorders”[Mesh Terms]) AND (“autistic disorder”[Mesh Terms])	

In addition, the type of study, characteristics of the population studied, description of the intervention and its duration, outcome measures, assessment tools, and qualitative data were also considered. We excluded studies with patients who have some other disease accompanied by ASD. We adopted the following keywords to search the articles: clinical trials with ASD, autism, autism spectrum disorder, Asperger's Syndrome, randomized blind clinical trial with ASD, ASD therapies, Asperger Syndrome therapies.

Two researchers read the abstracts of the primarily selected articles considering inclusion and exclusion criteria. When the selection of an article was not a consensus, an independent researcher gave the final decision on the use of the article(s).

After the selection phase, the articles were read in full and a syste-

matic and standardized approach was adopted to identify key ideas, methodology, main results, and conclusions. We made a qualitative analysis of the bibliographic materials and a synthesis accompanied by a critical discussion of the collected material.

Results (Review)

Table 2 presents all articles about drugs included in this review [5-26].

Risperidone versus placebo

In a randomized placebo-controlled study of risperidone [5], 23 children between 2.5-6 years of age were diagnosed with an ASD. Eleven children treated with risperidone demonstrated greater improvement in autism symptom ratings when compared to placebo controls (12 participants) after 6 months. Changes in autism severity scores from baseline to 6-month follow

up for the risperidone group was 8% compared to 3% for the placebo group. The most common adverse events seen were transient sedation, increased appetite, and hypersalivation in both groups, equally. Moreover, there was a trend toward greater elevations in leptin levels among subjects on risperidone.

A randomized, double-blind, placebo-controlled trial including children between 5-12 years who had diagnosis of autism (Diagnostic and Statistical Manual of Mental Disorders IV-text revision, DSM IV-TR) and a score of 12 or higher on the Aberrant Behavior Checklist-Community (ABC-C) showed that an 8-week intake of increasing risperidone doses (from 0,01 to 0,06 mg/kg/day) reduced significantly the score when compared to the placebo group [mean change (\pm standard deviation, SD): -13.4 (1.5) versus -7.2 (1.4), $p < 0.05$; ES = -0.7].

Adverse events were reported, mainly in the treatment group: somnolence, upper respiratory infection, rhinitis, fever, increased saliva, coughing, increased appetite, anorexia, influenza-like symptom, and weight increase in two risperidone users. The authors concluded that despite the adverse effects, the drug significantly improved behavioral problems associated with autism [6]. A two-part study of risperidone in children ages 5 to 17 years with autism accompanied by

severe tantrums, aggression, and/or self-injurious behavior who showed a positive response in an earlier 8-week trial [6].

Initially, 63 children were included, receiving a mean risperidone dose of 1.96 mg/day at entry, remaining stable during the 16 weeks of treatment. Small and clinically insignificant changes on the Aberrant Behavior Checklist-Irritability (ABC-I) subscale were observed. One patient presented side-effects. In the second phase, 32 patients were included in an 8-week randomized, double-blind, placebo-substitution study of risperidone withdrawal. The side-effects relapse rates were 62.5% for gradual placebo substitution and 12.5% for continued risperidone; this difference was statistically significant [6].

The authors conclude that Risperidone presented persistent efficacy and good tolerability for intermediate-length treatment of children with autism characterized by tantrums, aggression, and/or self-injurious behavior. It is expected a rapid return of disruptive and aggressive behavior in most subjects with the interruption of the treatment [7].

Table 2. Description of clinical studies related to therapeutic approaches to the treatment of autism.

Risperidone					
Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[5]	Mean daily final dose was 1.14 mg risperidone versus 1.38 mg placebo.	24	Randomized, double blind placebo-controlled trial; n = 24 with ages between 2.5 and 6 years	The change in autism severity scores from baseline to 6-month follow up for the risperidone group was 8% compared to 3% for the placebo group. Moreover, there was a trend toward greater elevations in leptin levels among subjects on risperidone.	Weight gain, hypersalivation, and elevations in prolactin levels and low levels of sedation.
[6]	Risperidone (1.0 mg/ml) or placebo Risperidone was initiated at 0.01 mg/kg/day, increased to 0.02 mg/kg on day 3. Risperidone could finally be increased by up to 0.02 mg/kg/day steps, to a maximum total daily dosage of 0.06 mg/kg/day	8	Randomized, double-blind, placebo-controlled trial. n = 5-12 years who had a diagnosis of autism (DSM IV-TR) and a score of 12 or higher on the ABC-C.	Risperidone [mean dose: 1.37 mg/day (0.7)] resulted in significantly greater reduction from baseline to endpoint in ABC-I versus placebo [mean change (\pm SD): -13.4 (1.5) versus -7.2 (1.4), $P < 0.05$; ES = -0.7].	Adverse events were reported for 100% of subjects treated with risperidone and 71% with placebo. The most common AE was somnolence, risperidone (74%) and placebo (7%). Other AEs that occurred in more than 10% of risperidone-treated subjects were: upper respiratory infection (41% versus 18% with risperidone and placebo, respectively); rhinitis (26% versus 7%); fever (26% versus 18%); increased saliva (15% versus 4%); coughing (15% versus 11%); vomiting (11% versus 21%); increased appetite (11% versus 4%); anorexia (11% versus 4%); and influenza-like

				symptoms (11% versus 4%). Weight increase was reported as an AE by two risperidone and no placebo subjects.
[7]	<p>Part I: the maximum risperidone dose was 2.5 mg/day for children between 15 and 45 kg and 3.5 mg/day for children weighing above 45 kg.</p> <p>Part II: the total daily dose increased up to a maximum of 3.5 mg/day for children weighing 15-45 kg and up to 4.5 mg/day for children above 45 kg.</p>	24	<p>A multisite, two-part study in children ages 5 to 17 years. Part I: a double-blind, placebo-controlled trial with parallel groups and n = 63. Part II: an open-label risperidone treatment offered to placebo nonresponders with n = 32.</p>	<p>Data from this study suggest that risperidone is a well-tolerated and effective treatment for up to 6 months for children with autism complicated by tantrums, aggression, and self-injury. As measured by the primary indices of response, the CGI improvement scale and the Aberrant Behavior Checklist irritability subscale, improvements associated with risperidone administration were maintained in over 80% of the subjects, with very good tolerability.</p> <p>A mild to moderate increased appetite, tiredness, and/or drowsiness, were common. One subject withdrew because of an adverse event (constipation). The subjects showed a 6-month weight increase of 5.1 kg (SD = 3.6) (paired t = 7.46, df = 31, P < 0.001), which was significantly greater (P < 0.001) than the amount expected based on available developmental norms.</p>
[8]	<p>The double-blind, placebo-controlled trial: dose range of risperidone = 0.5-3.5 mg/day, mean = 1.8 mg/day (SD = 0.7) or placebo.</p> <p>The open-label continuation study: mean daily dose of risperidone was 2.0 mg (SD = 1.2). Over the course, there</p>	24	<p>A double-blind, placebo-controlled trial (n = 101) and an open-label continuation study (n = 63) of risperidone for children and adolescents with autism between the ages of 5 and 17 years.</p>	<p>Risperidone led to significant improvements in the restricted, repetitive, and stereotyped patterns of behavior, interests, and activities of autistic children but did not significantly change their deficit in social interaction and communication</p> <p>Not mentioned.</p>

	was a modest increase (6%) to a final mean daily dose of risperidone of 2.1 mg (SD = 0.8).				
[9]	The risperidone dose was based on body weight. The maximum allowed dose was 1.25 mg/day for those weighing 20 to < 45 kg, and 1.75 mg/day for those weighing ≥ 45 kg.	26	An OLE study with 96 patients between the ages of 5 and 17 years.	The study suggests that risperidone is a well-tolerated and effective treatment. Patients experienced some additional improvement in irritability and related behaviors.	The most common (≥ 5% frequency in the total group) side effects were increased appetite (11% [n = 9]); increased weight and vomiting (9% [n = 7] each); sedation, pyrexia, and upper respiratory tract infection (8% [n = 6] each); nasopharyngitis (6% [n = 5]); and somnolence and fatigue (5% [n = 4] each). Extrapyramidal side effects were reported in 6 (8%) patients. Increase in mean weight (11%-15%) and body mass index (5%-10%) occurred; one patient discontinued because of weight increase.
[10]	Risperidone 1-3; Ginkgo T.D. was 80 for patients under 30 kg and 120 for patients above 30 kg.	10	A double-blind placebo-controlled trial; n = 47 with ages between 4 and 12 years	The association helped with Irritability; Lethargy; Social Withdrawal Stereotypic; It did not help for: Hyperactivity; Noncompliance; Inappropriate Speech.	Ginkgo biloba was relatively safe and well tolerated.
[11]	The dose of risperidone was up to 1 mg/day for	10	Randomized, double-blind, placebo-controlled, parallel-group	The galantamine-treated patients showed significantly greater	Gastrointestinal symptoms, which are frequently seen with cholinergic

<p>children weighing < 20 kg and 2 mg/day for those with a body weight > than 20 kg, receiving either galantamine (up to 24 mg/day) or placebo, in addition to risperidone (up to 2 mg/day)</p>		<p>study, n = 40 aged 4–12 years who had a diagnosis of autism (DSM IV-TR) and a score of 12 or higher on the ABC-C</p>	<p>improvement in the Irritability (P = 0.017) and Lethargy/Social Withdrawal (P = 0.005) subscales than the placebo group.</p>	<p>interventions.</p>
<p>The dose of risperidone was titrated up to 2 mg/day during the first 2 weeks for children between 10 and 40 kg (0.25 mg starting dose with increment in the first 2 weeks). The maximum dose for children < 40 kg was 2 mg, and for those > 40 kg was up to 3 mg/day.</p>	8	<p>Randomized double blind clinical trial, n = 59 children, and adolescents with autism spectrum disorders.</p>	<p>Both medications lowered ABC scores for 2 months. Irritability score decreased from 26.2 (4.1) to 14.6 (5.5) in the aripiprazole group during this trial. The score in the risperidone group decreased from 21.5 (7.4) to 12.5 (5.4). The safety and efficacy of aripiprazole (mean dose 5.5 mg/day) and risperidone (mean dose 1.12 mg/day) were comparable.</p>	<p>One patient with epilepsy was in an aripiprazole group and dropped out of the trial. One patient dropped out because of severe crying and agitation after taking risperidone. The most common adverse effects in the aripiprazole and risperidone groups were increased appetite (34.5 versus 40.0%), increased drooling (31.0 versus 40.0%), and drowsiness (20.7 versus 16.7%, respectively). Only two patients withdrew from the trial because of adverse effects.</p>
<p>The dose of aripiprazole was titrated up to 10 mg/day over 2 weeks (1.25 mg/day starting dose). The maximum dose of aripiprazole for children < than 40 kg was up to 10 mg/day and up to 15 mg/day for children > 40 kg.</p>				

[13]	<p>The starting dose of aripiprazole was 2 mg/day, which could be increased to a maximum dose of 15 mg/day. The initial dose of risperidone for children weighing 20-45 kg was 0.25 mg/day and could be gradually increased to a maximum dose of 2.5 mg/day. A slightly accelerated dosage was allowed for children who weighed more than 45 kg to a maximum dosage of 3.0 mg/day.</p>	10	<p>Randomized, double-blind, parallel-group study with 61 patients aged between 6-17 years treated with 2 weeks of placebo before random assignment to receive aripiprazole (n=31) or risperidone (n=30).</p>	<p>Both drug groups sat all assessment periods showed highly significant decreases in ABC-I scores compared with baseline. At weeks 3 and 6 weeks ($p<0.05$) the improvements in the risperidone group became more significant compared to the aripiprazole group. After 10 weeks, mean CGI-S scores were significantly lower for both the aripiprazole (3.33) and risperidone (3.48) groups compared with baseline (4.87 and 4.60, respectively; $P < 0.001$).</p>	<p>By week 10 of the study, 61% of the aripiprazole group and 77% of the risperidone group experienced one or more adverse events that were attributed to receiving study medication. Weight gain was more frequent in the risperidone group (70% versus 26%).</p>
[25]	<p>Risperidone was started with a daily dose of 0.25 mg in patients weighing <20 kg and 0.5 mg in those weighing ≥ 20 kg and increased stepwise to reach a maximum of 1 mg (<20 kg), 2.5 mg (20–45 kg), and 3.5 mg (>45 kg). Sulforaphane was administered at a daily dose of 50 μmol (≤ 45 kg) or 100 μmol</p>	80	<p>A randomized, double-blind, placebo-controlled clinical trial with 60 drug-free patients aged 4–12 years were randomly assigned to one of two groups receiving risperidone plus sulforaphane or placebo.</p>	<p>Compared to the placebo group, ASD patients in the sulforaphane group showed greater improvements in Irritability score (primary outcome measure; $p=0.001$) and Hyperactivity / Noncompliance score (secondary outcome measure; $p=0.015$), and significant Time \times Treatment effect for Irritability ($p=0.007$) and Hyperactivity/Noncompliance ($p=0.008$).</p>	<p>Increased appetite (13.3%) and headache (13.3%) in the sulforaphane group and diarrhea (20%) in the placebo group</p>

(>45 kg).

Omega-3

Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[14]	<p>The treatment group received 3 months of an oral omega-3, -6, and -9 fatty acid supplement that included, as a single liquid daily dose of 2.5 ml, 338 mg EPA, 225 mg DHA, 280 mg total omega-6 fatty acids (including 83 mg GLA), and 306 mg total omega-9 fatty acids.</p> <p>The placebo group received 3 months of oral canola oil, also as a single liquid daily dose of 2.5 ml, which contained 129 mg palmitic acid, 39 mg stearic acid, 513 mg linoleic acid, 225 mg alpha-linolenic acid (ALA, omega-3), and 1346 mg oleic acid. Both oils were lemon-flavored (lemon oil flavor added</p>	12	Randomized 31 children to receive an omega-3 and -6 supplement or a placebo for 3 months and measured their language abilities at baseline and after supplementation.	<p>Gesture use, but not word production, increased for children in the treatment group more than children in the placebo group. These results suggest possible effectiveness of omega-3 and -6 supplementation for language development in children at risk for ASD.</p>	Not mentioned.

	to the placebo by NCH Investigational Drug Services (IDS)), and both products were packaged identically and distributed to the families through the hospital pharmacy.			
[15]	<p>Omega-3 fatty acids or an identical placebo.</p> <p>Omega-3 fatty acids were provided as orange-flavored pudding packets (Coromega, Vista, California) containing 650 mg of omega-3 fatty acids, including 350 mg of EPA and 230 mg of DHA, given twice daily for a daily dose of 1.3 g of omega-3 fatty acids (and 1.1 g of DHA-EPA).</p>	12	<p>A pilot randomized controlled trial to determine the feasibility and initial safety and efficacy of omega-3 fatty acids (1.3 g/day) for the treatment of hyperactivity in 27 children ages 3-8 with ASD. The patients were recruited from the outpatient autism clinic at the MIND Institute (University of California, Davis).</p>	<p>There was a greater reduction in hyperactivity in the treatment compared to the placebo group, which corresponds to a standardized effect size of 0.38 and is a small treatment effect. Only one cytokine (TNFα) revealed a statistically significant difference in the mean change over the course between groups.</p> <p>Increased appetite (11% [n = 9]); increased weight and vomiting (9% [n = 7] each); sedation, pyrexia, and upper respiratory tract infection (8% [n = 6] each); nasopharyngitis (6% [n = 5]); and somnolence and fatigue (5% [n = 4] each).</p>
[16]	<p>The experimental medication per day were seven pale yellow, 1-g gelatin capsules of menhaden fish oil, each containing 120 mg EPA and 100 mg DHA plus 1 mg of vitamin E; the</p>	6	<p>A randomized, double-blind, placebo-controlled 6-week pilot trial investigating the effects of omega-3 fatty acid supplementation in 13 children (aged 5 to 17 years) with autistic disorders accompanied by severe tantrums, aggression, or self-</p>	<p>Although the study did not present a significant difference between the two groups, it was observed a tendency (P = 0.098) for greater remission of hyperactive symptoms in the experimental group as compared with the placebo group.</p> <p>One individual from the placebo group withdrew from the trial after 2 weeks because of gastrointestinal complaints and lack of symptom improvement. Mild adverse events reported included fever and moderate stomach upsets, including diarrhea in the experimental group</p>

	<p>placebo were seven gelatin capsules of 1 g of coconut oil that were of similar shape and size and also contained 1 mg of vitamin E, as well as 1 mg of fish oil to mimic fish taste. The daily dose was 1.5-g omega-3 fatty acids.</p>	<p>injurious behavior</p>	<p>and headache and insomnia in the placebo group.</p>
[17]	<p>Participants started at 0.75 g of EPA + DHA (1.875 ml once a day) of liquid formulation, either NutraSea HP or placebo. If this was well tolerated, the dose was doubled to 1.5 g (3.5 ml) after 2 weeks, as per Health Canada guidelines for maximum dose for this age group.</p>	<p>24</p> <p>A total of 38 children (28 males and 10 females), 2 to 5 years of age with ASD were randomized into a placebo-controlled trial, between December 2010 and December 2013.</p>	<p>There was no statistically significant week by group effect on either adaptive function ($P = 0.09$) or language ($P = 0.6$). Omega-3s were relatively well tolerated. Changes in cytokines during the study did not significantly correlate with treatment response. This study does not support high dose supplementation of omega-3 fatty acids in young children with ASD.</p> <p>Potential GI distress, known to be associated with these supplements, may have been underreported by parents but captured as reports of externalizing behaviors. The link between GI distress and externalizing behaviors in this population has been well established. However, there was no evidence of increase in GI adverse events in the active group even when the group was restricted to non-verbal individuals. Of note though, 8/19 participants in the omega3 group had GI distress at baseline, and only 1/19 in the placebo group had GI distress at baseline.</p>

Bumetanide

Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[18]	Eighty-eight patients with ASD spanning across the entire pediatric population (2–18 years old) were subdivided in four age groups and randomized to receive bumetanide (0.5, 1.0 or 2.0 mg twice daily) or placebo for 3 months.	12	It was performed a double-blind, randomized, placebo-controlled, multisite dose-ranging study to assess the efficacy, safety, pharmacokinetics, and the optimal dose of bumetanide in children and adolescents with ASD (n = 88).	The difference between all treatment groups in reduction of global SRS score was statistically significant with the Kruskal-Wallis test ($P = 0.02$). The amelioration was greater than 10 points at the three doses tested with the highest reduction in the 2.0 mg bumetanide treatment group (-21.8 ± 19.8 versus -1.55 ± 20.38 , respectively for bumetanide and placebo). Among the SRS subscales, statistically significant differences were observed in the subcategories social communication ($P = 0.039$) and restricted interests and repetitive behavior ($P = 0.002$) but not in social cognition, social motivation or social awareness.	The most frequent treatment for emergent adverse event included hypokalemia, diuresis and loss of appetite, dehydration, and asthenia. The frequency and incidence of adverse event were directly correlated with the dose of bumetanide.
[19]	Patients between 3-11 years old, who met the ICD-10 (World Health Organization 92) criteria for autistic disorders, were randomly assigned to receive either	16	It is a double-blind, randomized, placebo-controlled trial. At the end of the 3-month double-blind phase, all children were removed from treatment during a 1-month wash-out period. (n = 60)	The CARS test revealed a statistically significant amelioration of total score ($P = 0.004$). After 90 days of bumetanide, the treated groups shifted from severe (CARS > 36.5) to mild or medium severity (< 36.5). In contrast, there was no	Side effects were restricted to an occasional mild hypokalemia (3.0-3.5 mM $1-1 K^+$) that was treated with supplemental potassium. The only child that was removed from the trial because of eczema was on placebo. Two children were removed from the

		bumetanide or placebo (0.5 mg twice a day).		significant difference in the placebo group between D0 and D90. The number of items > 3 shifted from 9.6 to 6.2 in the bumetanide-treated group and from 9.8 to 8.1 in the placebo group ($P = 0.017$). At the CGI test, 77.7% of children had a small or significant amelioration with the diuretic to be compared with only 33.3% in placebo. Conversely, 22.2% had no amelioration with the diuretic and 66.6% in placebo.	trial on parental decision because of bed-wetting and identified at the end of the trial to have been treated with placebo (one) and bumetanide (one). Two children were removed from the trial consequently to hyperactivity due to withdrawal from their medication (methylphenidate and risperidone); although that was stopped 3 weeks before the trial.
[20]	12	Patients (mean age of 4.5 years) were randomly divided into two groups: A single treatment group ($n = 28$) and a combined treatment group ($n = 32$). The combined treatment group received ABA training combined with oral bumetanide (0.5 mg twice a day). The single treatment group received ABA training only.	Sixty children diagnosed with autism were randomly divided into two groups: A single treatment group ($n = 28$) and a combined treatment group ($n = 32$).	Prior to intervention(s) no statistically significant differences in scores on the ABC, CARS, SI, or GI were found between the two groups. Total scores of the ABC, CARS, and SI were decreased in both groups after 3 months ($P < 0.05$) compared with the scores prior to treatment. The total scores of the ABC and the CGI were significantly ($P < 0.05$) lower in the combined treatment group than in the single treatment group. Although the total and item scores of the CARS in the combined treatment group were lower than in the single treatment group after a 3-month intervention, they did not	No adverse effects of bumetanide were observed.

reach statistical significance.

Intranasal oxytocin

Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[21]	Test the efficacy and tolerability of 4-wk intranasal OXT treatment (24 International Units, twice daily) in 32 children with ASD, aged 6-12 years	4	Double-blind, randomized, placebo-controlled, parallel design to test the efficacy and tolerability of 4-week intranasal OXT treatment (24 IU, twice daily) in 32 (27 male, 5 female) children with ASD, aged 6-12 years.	The present clinical trial showed that OXT treatment enhances social abilities in children with ASD and that individuals with pretreatment OXT signaling deficits may stand to benefit most from OXT administration. Although confirmatory evidence from larger-scale, biomarker stratified OXT treatment trials is needed, our findings suggest that OXT treatment has the potential to reduce suffering in ASD patients by enhancing quality of life through improved social abilities.	OXT treatment in children with ASD was well tolerated with minimal side effects. There were no significant differences in the adverse event rates reported in the OXT-treated and the placebo-treated groups as assessed by parent ratings on the DOTES.
[22]	Thirty-one children with autism received 12 IU of oxytocin and placebo nasal spray morning and night (24 IU per day) for 5 weeks, with a 4-week washout period between each treatment.	20	They investigated the efficacy, tolerability, and safety of oxytocin treatment in young children with autism using a double blind, randomized, placebo-controlled, crossover, clinical trial.	Among children with autism aged between 3 and 8 years, a 5-week course of oxytocin nasal spray improved caregiver-rated social responsiveness compared with placebo. Oxytocin treatment was found to be well tolerated and there were no significant differences in the report of adverse events	Overall, nasal spray was well tolerated, and the most common reported adverse events were thirst, urination, and constipation.

 between conditions.

AB-2004

Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[23]	Doses were different according to each children's weight and study week. The lowest dose was 0.5g and highest was 2.0g.	8	An open label, single-cohort, multiple-ascending-dose clinical trial; n=30 between 12 to 17 years.	Reduction in specific urinary and plasma levels of gut bacterial metabolite, improvements in multiple exploratory behavioral endpoints, most significantly in anxiety and irritability, as well as GI health.	None were reported

Folinic Acid

Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[24]	High dose folinic acid (2 mg/kg per day, maximum 50 mg per day; n=23) or placebo (n=25). Children were subtyped by glutathione and folate receptor- α autoantibody (FRAA) status	12	Double-blind placebo control setting. Forty-eight children (mean age 7 years 4 months; 82% male) with ASD and language impairment were randomized	Improvement in measures of verbal communication as compared with placebo.	There were no significant group differences between adverse event frequencies.

Prednisolone

Study	Intervention (mg/day)	Time (weeks)	Design/participants	Outcome	Side effects
[26]	An initial dose of 1 mg/kg/day for the first eight weeks, 1mg/kg/day every other day from the 9th to 16th weeks and gradually reduced dose on alternate days from there, with weekly subtraction of 10% of the dose between the 17th and 20th weeks of 15% between the 21st and 24th week.	24	A double-blinded, randomized, placebo-controlled clinical trial in children with autistic spectrum disorder from in 38 patients of ages between 3-7 years.	An increase in global Language Development Assessment (ADL) score and in Child Language Test in Phonology, Vocabulary, Fluency and Pragmatics (ABFW) score.	Two patients had hypertension, five had hyperglycemia and two had varicella.

The efficacy of Risperidone for the core symptom domains of autism was evaluated in an 8-week double-blind, placebo-controlled trial (n = 101) and 16-week open-label continuation study (n = 63) compared to placebo [8]. Risperidone led to a significantly greater reduction in the overall score on the Ritvo-Freeman Real Life Rating Scale, as well as the scores on the subscales for sensory motor behaviors (subscale I), affectual reactions (subscale III), and sensory responses (subscale IV) [8].

Risperidone also resulted in significantly greater reductions in scores on the Children's Yale-Brown Obsessive Compulsive Scale and Vineland maladaptive behavior domain. This pattern of treatment response was maintained for 6 months. No side effects were mentioned by the authors. Being so, they concluded that Risperidone led to significant improvements in the restricted, repetitive, and stereotyped patterns of behavior, interests, and activities of autistic children but did not significantly change their deficit in social interaction and communication [8].

In a 6-month (26 week) open-label extension (OLE) study, 5-17 years of age patients received risperidone in low-dose (0.125 mg/day [20 to < 45 kg]), medium-dose (0.175 mg/day [> 45 kg]) or high-dose (1.25 mg/day - 20 to < 45 kg] or 1.75 mg/day [> 45 kg]) or placebo in order to test the long-term safety and

efficacy of the drug in treating irritability and related behaviors in children and adolescents with autistic disorders [9].

In the high-dose group, significant improvements in ABC-I (primary endpoint) were observed, as well as in Clinical Global Impressions-Severity (CGI-S) and Children's Yale-Brown Obsessive Compulsive Scale scores. Also, adverse effects such as somnolence, sedation and increased appetite occurred more frequently in high-dose groups. So, the authors concluded that patients experienced some additional improvement in irritability and related behaviors [9].

Adjuvant medicines

Ginkgo biloba affects the neurotransmitter system and, due to its antioxidant properties, could impact the pathogenesis of autism spectrum disorder. In a double blinded clinical trial, 47 outpatients ages between 4 and 12 years with a diagnosis of autism were randomly assigned to one of two groups: one group received risperidone, 1-3 mg/day, plus Ginko T.D 80 mg/day for patients under 30 kg and 120 mg/day for patients above 30 kg, and the other received risperidone plus placebo [10].

A randomized, double-blind, placebo-controlled trial aimed to evaluate the possible effects of galantamine, an acetylcholinesterase inhibitor and an allosteric potentiator of

nicotinic receptors, as an augmentative therapy to risperidone in autistic children [11]. Forty outpatients aged 4-12 years with a diagnosis of autism and a score of 12 or higher on the ABC-C subscale were randomized to receive risperidone (up to 2 mg/day) in addition to galantamine (up to 24 mg/day) or placebo [10].

The galantamine-treated patients showed significantly greater improvement in the Irritability ($p=0.017$) and Lethargy / Social withdrawal ($p=0.005$) subscales than the placebo group. Side effects frequencies were similar in the two groups. The association of galantamine and risperidone was shown to be relatively effective and safe for some of the autism-related symptoms [10].

A randomized double blind controlled clinical trial compared the efficacy and safety of Aripiprazole and Risperidone for treating 59 children and adolescents with autism spectrum disorders for two months [12]. Both Aripiprazole (mean dose 5.5 mg/day) and risperidone (mean dose 1.12 mg/day) decreased similarly all the ABC subscales scores, including irritability and agitation, lethargy and social withdrawal, stereotypic behavior, hyperactivity and noncompliance, and inappropriate speech [12].

The most common adverse effects in the aripiprazole and risperidone groups were increased appetite (34.5%

versus 40.0%), increased drooling (31.0% versus 40.0%), and drowsiness (20.7% versus 16.7%, respectively). Only two patients withdrew from the trial because of adverse effects. Hence, aripiprazole and risperidone are broadly equivalent choices for treating irritability in children with autism [12].

In the trial Biomarkers in Autism of Aripiprazole and Risperidone Treatment (BAART) study, a randomized double-blind parallel-group study, the authors aimed to provide scientific evidence for an efficient and safe initial pharmacotherapy in patients with autism [13]. Sixty-one patients were randomized to the study drug. All patients were treated with 2 weeks of placebo before random assignment to receive aripiprazole (31 patients) or risperidone (30 patients). Both drug groups at all assessment periods showed highly significant decreases in ABC-I scores compared with baseline [13].

At weeks 3 and 6 weeks ($p<0.05$) the improvements in the risperidone group became more significant compared to the aripiprazole group. After 10 weeks, mean CGI-S scores were significantly lower for both the aripiprazole (3.33) and risperidone (3.48) groups compared with baseline (4.87 and 4.60, respectively; $p<0.001$). Most of the 51 patients at 10 weeks (78%) were rated as very much or much improved on the CGI-Improvement scale. No

significant differences in improvement were observed between treatments with respect to CGI-Improvement scores. By week 10 of the study, 61% (19/31 patients) of the aripiprazole group and 77% (23/30 patients) of the risperidone group experienced one or more adverse events that were attributed to receiving study medication. Weight gain was more frequent in the risperidone group (70% versus 26%). No serious adverse events occurred. Hence, both drugs showed to be safe and efficient to improve ABC-I scores [13].

A randomized, double-blind, placebo-controlled trial aimed to evaluate the possible effects of risperidone combined with sulforaphane in autistic children [25]. Sixty drug-free patients aged between 4 to 12 years were randomly assigned to receive a daily dose of 0.25 mg in patients weighing <20 kg and 0.5 mg in those weighing ≥20 kg, increasing stepwise to reach a maximum of 1 mg (<20 kg), 2.5 mg (20–45 kg), and 3.5 mg (>45 kg) of risperidone plus a daily dose of 50 µmol (≤45 kg) or 100 µmol (>45 kg) of sulforaphane or placebo [25].

The sulforaphane treated group showed greater improvements in Irritability score ($p=0.001$) and Hyperactivity / Noncompliance score ($p=0.015$), and significant Time × Treatment effect for Irritability ($p=0.007$) and Hyperactivity / Noncompliance ($p=0.008$). However, no difference was

seen in: Lethargy/Social Interaction score, Stereotypic Behavior score, Inappropriate Speech score, and frequency of adverse events. Side effects in sulforaphane patients were an increase in appetite (13.3%) and headache (13.3%) and diarrhea (20%) in the placebo group [25].

Omega-3 versus placebo

In a randomized placebo-controlled trial study [14], 31 children were randomized to receive an omega-3 and omega-6 supplement or a placebo for 12 weeks and measured language abilities at baseline and after supplementation in children born preterm who presented ASD symptoms. Despite the limitation of the sample size for this study, the authors pointed out that gesture use, but not word production, increased for children in the treatment group more than children in the placebo group [14].

However, the side effects were not mentioned. So, they concluded that, as gesture use is an important early indicator of language development, results suggest possible effectiveness of omega-3 and -6 supplementation for language development in children at risk for autism spectrum disorder [14].

In a pilot, randomized, controlled trial, authors wanted to determine the feasibility, safety, and efficacy of omega-3 fatty acids for the treatment of hyperactivity in 27 autistic children [15].

They were between 3-8 years old and were assigned to 12 weeks treatment with an orange-flavored pudding packet containing placebo or 650 mg of omega-3, 350 mg of EPA and 230 mg of DHA, given twice daily for a daily dose of 1.3 g of omega-3 fatty acids [15].

That said, the authors observed a great reduction in hyperactivity in the treatment group (effect size of 0.38) compared to the placebo one. Only one cytokine (TNFa) revealed a statistically significant difference in the mean change over the course between groups. However, it showed an increase in appetite, an increase in weight and vomiting, sedation, pyrexia, upper respiratory tract infection, nasopharyngitis, somnolence and fatigue [15].

A double-blind randomized, placebo-controlled pilot study investigated the effects of omega-3 fatty acids supplementation in 13 of 25 pre-selected children, aged between 5 and 17 years old, with autistic disorders accompanied by severe tantrums, aggression, or self-injurious behavior [16]. In spite of having several limitations as (1) the small number of subjects and relatively short intervention period, (2) lack of lipid composition analyses in plasma or erythrocytes, (3) preselection of children on the basis of a high score on ABC irritability as entry criterion without clear identification of irritability as the

main target of omega-3 supplementation, and (4) the fact that in the primary analysis between-group differences failed to reach statistical significance, it was observed a tendency for greater remission of hyperactive symptoms in the experimental group as compared with the placebo group ($p=0.098$) [16].

Moreover, the effect sizes of medium to large magnitudes on three of five ABC subscales emphasize superiority of omega-3 fatty acids over placebo. Mild adverse events reported included fever in the experimental group and headache and insomnia in the placebo group [16].

A 24-week placebo-controlled trial was developed to assess whether omega-3 fatty acids (NutraSea HP) are effective in improving autism symptom severity and externalizing symptoms [17]. Thirty-eight children, aged between 2 and 5 years old, 28 males and 10 females were enrolled. The authors figured out that there was no significant difference between groups in Pervasive Developmental Disorder Behavior Inventory (PDDBI) autism composite scores and the same result was observed for the Behavior Assessment System for Children-Second Edition (BASC-2), the Adaptive Functioning Composite standard score of the VABS, the Preschool Language Scale fourth edition (PLS-4), and the CGI-I score [17].

The cytokines' changes during the study do not significantly correlate with treatment response. In addition, this study does not support high dose supplementation of omega-3 fatty acids in young children with ASD. The potential gastrointestinal distress, known to be associated with these supplements, may have been underreported by parents but captured as reports of externalizing behaviors [17].

The link between GI distress and externalizing behaviors in this population has been well established. However, there was no evidence of increase in GI adverse events in the active group even when the group was restricted to non-verbal individuals. Of note though, 8/19 participants in the omega-3 group had GI distress at baseline, and only 1/19 in the placebo group had GI distress at baseline [17].

Bumetanide versus placebo

In a double-blind, randomized, placebo-controlled, multisite dose-ranging trial to assess the efficacy, safety, pharmacokinetics, and the optimal dose of bumetanide, 88 children and adolescents between 2 to 18 years old with autism spectrum disorder (ASD) were allocated in four age groups and randomized to receive 0.5, 1.0 mg or 2.0 mg of bumetanide twice daily or placebo for 12 weeks [18]. Reductions in the global Social Responsiveness Scale

(SRS) score was observed in the three groups, with the highest reduction in the 2.0 mg bumetanide treatment group (-21.8 ± 19.8 versus -1.55 ± 20.38 , respectively for bumetanide and placebo). The best results were observed in social communication ($p=0.039$) and restricted interests and repetitive behavior ($p=0.002$) but not in social cognition, social motivation, or social awareness.

A double-blind, randomized placebo-controlled trial studied 54 participants (27 treated and 27 placebo) and observed that bumetanide significantly reduced the Childhood Autism Rating Scale (CARS) (D90 D0; $p=0.004$ treated versus placebo), Clinical Global Impressions ($p=0.017$ treated versus placebo) and Autism Diagnostic Observation Schedule values when the most severe cases were removed (Wilcoxon test: $p=0.031$; Student's t test: $p=0.017$) [19].

The CARS test revealed a statistically significant amelioration of total score ($p=0.004$). After 90 days of bumetanide, the treated groups shifted from severe (CARS > 36.5) to mild or medium severity (< 36.5). In contrast, there was no significant difference in the placebo group between D0 and D90. The number of items > 3 shifted from 9.6 to 6.2 in the bumetanide-treated group and from 9.8 to 8.1 in the placebo group ($p=0.017$ bumetanide-treated group vs placebo group). At the CGI test, 77.7%

of children had a small or significant amelioration with the diuretic to be compared with only 33.3% in placebo. It was observed an occasional mild hypokalemia (3.0-3.5 mM l-1 K+) treated with supplemental potassium. Larger cohorts are required to evaluate its effects on atypical autism and unspecified pervasive developmental disorders [19].

The therapeutic effects of a combined 12-week treatment with bumetanide and applied behavior analysis (ABA) was investigated in a randomized trial with 60 children with ASD and mean age of 4.5 years old [20]. The participants were divided into two groups: a single treatment group (n=28), receiving ABA training combined with an oral 0.5 mg bumetanide dose twice a day, and a combined treatment group (n=32), receiving ABA training only.

The authors observed a decrease in Aberrant Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS) and severity of disease (SI) scores in both groups after 3 months ($p<0.05$) compared with the scores prior to treatment. The total scores of the ABC and the Clinical Global Impressions (CGI) were significantly ($p<0.05$) lower in the combined treatment group than in the single treatment group. The drug was well tolerated with no side effects.

Intranasal oxytocin versus placebo

The efficacy and tolerability of intranasal oxytocin (OXT) 4-week treatment was investigated in a double-blind, randomized, placebo-controlled, parallel design trial with 32 children with autism, 27 male and 5 female, aged between 6 and 12 years old [21]. The authors described that OXT's effects were specific to social functioning and did not reduce anxiety symptoms. Individuals with the lowest pretreatment OXT concentrations showed the greatest social improvement. The drug was well tolerated with minimal side effects, like those observed in the placebo-treated groups.

In a double-blind randomized placebo-controlled crossover clinical trial the authors investigated the efficacy, tolerability, and safety of oxytocin treatment in young children with autism [22]. Thirty-one children with autism, aged between 3 and 8 years, were randomized in two consecutive treatment conditions groups to receive 12 international units (IU) of oxytocin and placebo nasal spray morning and night (24 IU per day) for 5 weeks, with a 4-week washout period between each treatment. Oxytocin nasal spray improved caregiver-rated social responsiveness compared with placebo during the treatment period. The drug was well tolerated and there were no

significant differences in the report of adverse events between conditions [22].

AB-2004

An open-label, single-cohort, multiple-ascending-dose clinical trial evaluated the safety of AB-2004, which is GI restricted oral adsorbent, in adolescents with ASD and GI symptoms for 8 weeks [23]. Thirty participants between 12 to 17 years old received three doses per day of different amounts of AB-2004, according to their weight and the studies' week: ≥ 60 kg: 0.75 g (days 1-14), 1.5 g (days 15-28) and 2 g (days 29-56); between 50-59 kg: 0.75 g (days 1-14), 1.0 g (days 15-28), 1.75 g (days 29-56); between 40-49 kg: 0.5 g (days 1-14), 0.75 g (days 15-28), 1.5 g (days 29-56) and between 30-39 kg: 0.5 g (days 1-14), 0.75 g (days 15-28), 1.0 g (days 29-56) [23].

The authors figured out that the adsorbent has good safety and tolerability across all dose levels and no serious adverse events were identified. It showed significant reductions in specific urinary and plasma levels of gut bacterial metabolites, demonstrating likely target engagement. Furthermore, it was observed improvements in multiple exploratory behavioral endpoints, most significantly in anxiety and irritability, as well as GI health [23].

Folinic acid versus placebo

In a double-blinded placebo control setting [24], 48 children (mean

age: 7 years) with ASD and language impairment were randomized receiving placebo or high-dose folinic acid (2 mg/kg per day, maximum 50 mg per day) for 12 weeks. They were subtyped by glutathione and folate receptor- α autoantibody (FRAA) status.

Improvement in verbal communication, as measured by an ability-appropriate standardized instrument, was greater in the FRAA-positive participants receiving folinic acid, resulting in an effect of 7.3 (1.4,13.2) standardized points with a large effect size (Cohen's $d=0.91$), indicating that folinic acid treatment may be more efficacious in children with ASD who are FRAA positive. There were no significant group differences between adverse event frequencies [24].

Prednisolone versus placebo

In a double-blinded, placebo-controlled trial study [26], thirty-eight children were randomized to receive prednisolone or placebo for 24 weeks and evaluate language abilities in children with ASD. They received an initial dose of 1 mg/kg/day for the first eight weeks, 1mg/kg/day every other day from the ninth to 16th weeks and a gradually reduced dose on alternate days from there, with weekly subtraction of 10% of the dose between the 17th and 20th weeks, and of 15% between the 21st and 24th week [26].

The authors pointed out that the differences occurred especially in children younger than 5 years who had developmental regression. Thus, prednisolone increased the global Language Development Assessment (ADL) score ($p=0.0057$) and the Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics (ABFW) score ($p=0.004$, power=0.913). Despite the fact that two patients had hypertension, five had hyperglycemia, and two had varicella, the authors concluded that side effects did not affect the study and were manageable without any major difficulties [26].

Discussion

This narrative review identified the pharmacological interventions implemented in the treatment of children and adolescents with autism spectrum disorder (ASD) and evaluated the quality and effectiveness of these interventions, as well as the possible side effects already presented in the literature. A total of twenty-two studies, divided in: ten about risperidone, four about omega-3, three about bumetanide, two about intranasal oxytocin, one about AB-2004, one about folinic acid and one about prednisolone. In some of them, the drugs were used in combination with other medications, being adjuvant treatments.

The efficacy and safety of the drugs used for ASD are still limited.

Although most of the studies reported in this review have found positive effects of the drugs on the symptoms of autism, several limitations in the research design were identified. The most common ones were the quite small sample' size, the relatively short intervention period and the difference in ages, gender, and degree in the autism spectrum.

The literature shows that there is no drug that treats all the symptoms, but they have the capacity to reduce repetitive behaviors and stereotypes. inattention, irritability, hyperactivity, and impulsivity. There is no common sense about the minimum drug's dose that is needed to be taken for improving the symptoms or not developing side effects. Moreover, all the behavioral assessments were reported by parents or guardians, which may be slightly distorted.

When comparing risperidone and placebo, the results suggest that the evidence on the effects of this drug as a treatment to improve behavioral problems associated with autism is quite robust. Effects were observed, mainly, on changes in the stereotyped patterns of behavior of autistic children, meaning it was beneficial and efficient.

When comparing risperidone and adjuvant treatments, the literature has proved to be mixed and inconsistent depending on what was the adjuvant drug. The association between

risperidone and aripiprazole was positive when it comes to reducing irritability associated with AD. Adding galantamine to a risperidone was a safe augmentation strategy for managing some of the behavioral symptoms associated with autism. Ginkgo biloba treatment as adjuvant had significant improvement in ABC-C subscales scores, being safe and well tolerated. The association with sulforaphane exhibited a greater improvement in irritability and hyperactivity / noncompliance scores.

Furthermore, in relation to omega-3 and placebo, the studies demonstrated that the gesture use and the hyperactivity got a great reduction in the experimental group, suggesting an effectiveness with this supplementation.

When comparing bumetanide and placebo, the drug was well tolerated and safe, significantly reducing the sub-categories social communication, restricted interests, and repetitive behavior, in the SRS. The studies also mentioned that bumetanide significantly reduced the CARS, Clinical Global Impressions and Autism Diagnostic Observation Schedule.

The association of bumetanide and applied behavior analysis (ABA) treatment significantly lowered the total scores of the ABC and the CGI when compared to the ABA treatment alone.

Intranasal oxytocin, the other drug selected as treatment in children with ASD was well tolerated with minimal side effects. It enhances social abilities in children with ASD and individuals with pretreatment OXT signaling deficits may stand to benefit most from the administration of this drug.

The results of the AB-2004 study suggest that targeting gut-derived metabolites with an oral adsorbent is a safe and well-tolerated approach to improving symptoms associated with ASD, thereby emboldening larger placebo-controlled trials.

The study about folic acid found an improvement in verbal communication in non-syndromic ASD children receiving high doses of it compared to placebo, particularly in those participants who were positive for FRAAs. To finish, prednisolone's study showed an increase in language scores, especially in participants who were younger than five years, with a history of developmental regression.

Conclusions

In summary, based on the literature, it can be concluded that, in general, drugs commonly used to treat ADS are believed to be safe, despite some side effects being quite significant. There is no common sense regarding the minimum dose necessary to reduce symptoms and there is not a drug that

treats all of them. The choice of the medication(s) must be defined according to the symptoms and clinical responses.

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Conflict of interest: The author declares no conflicts of interest.

Acknowledgements: None.

Funding: None.

How to cite this article: Medeiros GM, Sepulveda MM, Gentile JKA, Braga ALF. Pharmacological approaches in the treatment of autism: a narrative review. *Brazilian Journal of Case Reports*. 2022 Oct-Dec;02(4):3-32.