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CLINICAL EFFICACY AND TOLERABILITY OF RISPERIDONE IN THE TREATMENT OF AUTISM SPECTRUM DISORDER IN CHILDREN: A LITERATURE REVIEW

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ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects social interaction, communication, and behavior. Children with ASD often face significant challenges, including irritability, aggression, and difficulties in social skills, which impacts their quality of life and daily functioning. Thus, the objective of this study is to synthesize the scientific literature on the use of risperidone in the treatment of autism spectrum disorder in children, analyzing the positive and adverse therapeutic effects reported in the literature. The research reviewed the existing literature on the use of risperidone in children with ASD, analyzing studies that report its therapeutic and adverse consequences. Efficacy data such as improvements in Clinical Global Impressions Improvement (CGI-I) scores and the incidence of side effects were considered. The results indicate that risperidone is effective in reducing irritability, aggression, and hyperactivity in children with ASD, with significant improvements seen in up to 60% of patients. However, side effects such as weight gain, sedation, and increased prolactin levels raise concerns about the safety of the treatment. Risperidone may be an option for the management of challenging behaviors in children with ASD, but its use should be carefully monitored due to potential adverse effects. The combination of pharmacological interventions with behavioral therapies may offer additional support in the treatment of ASD.

Keywords: Pharmacological interventions. Challenging behaviors. Child pharmacotherapy. Mental Disorder.

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INTRODUCTION

Autism spectrum disorder (ASD) is defined by the Brazilian Society of Pediatrics (SBP, 2019) as a clinically defined neurodevelopmental disorder that affects the development and social interaction of children, with different levels of severity and presentation (COIMBRA et al., 2020).

ASD originates in the first years of life, but its initial trajectory is not uniform (SBP, 2019). Characterized by communication deficits, restricted and repetitive patterns of behavior. The etiology of ASD is still unknown, but it is believed to be multifactorial, with genetic and neurobiological factors (VIANA et al., 2020). Among the different clinical spectrums, the disorder is a fusion of Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Unspecified (APA, 2013).

Worldwide, ASD affects the development and behavior of 1 in 160 children. However, prevalence may vary between countries and regions, reflecting the challenge in determining the exact prevalence of ASD, as diagnostic methods and criteria may vary in different geographic areas (POSSAMAI, 2021).

In Brazil, a prevalence of 2 million people with ASD is estimated, based on the global percentage of 1%, as described in the DSM-5 (APA, 2014). Despite the insipidity of epidemiological studies on ASD in the country, according to the School Census of Basic Education (BRASIL, 2019), carried out by the National Institute of Educational Studies and Research Anísio Teixeira (Inep), there was an increase of about 37% between 2017 and 2018 in the number of students with ASD enrolled in common classes in the country (BRASIL, 2022).

There are also studies, such as Rocha et al. (2019), which report a prevalence of ASD among children and adolescents ranging from 0.3% to 1%, that is, 1 in every 160 to 200 children, when analyzing samples of the population in different Brazilian municipalities and states. However, more studies and research are needed to obtain accurate and representative estimates for the whole of Brazil (PORTOLESE et al., 2017).

People with ASD may have a wide range of phenotypes, including: severe intellectual disability (ID) and poor performance in adaptive behavioral skills, or intelligence quotient (IQ) within the range considered normal, leading an independent life. Also the presence of comorbidities, such as hyperactivity, sleep and gastrointestinal system disorders (ZAFEIRIOU; VERVERI; VARGIAMI, 2007).

The diagnosis is made through observations of the child and interviews with parents and/or guardians, using standardized scales and screening instruments. The evaluation should be conducted by a multidisciplinary team covering different aspects, such as a thorough

examination of distinct physical characteristics, a neurological examination to measure the head circumference, and a skin examination using Wood's lamp (HODGES; FEALKO; SOARES, 2020).

The identification picture of ASD is based on deficits in communication and social interaction, the presence of restricted and repetitive behaviors, and irregular intellectual development (POSSAMAI, 2021).

Even with all the advances, diagnosis does not occur early and, for the most part, there is a high prevalence rate of ASD, demonstrating a growing need for effective therapeutic interventions (VIANA et al., 2020).

Although identification and access to intervention occur less frequently in certain social groups than in others, ASD manifests itself in individuals of different ethnicities or races and in all socioeconomic groups (SBP, 2019). It mainly affects children in early childhood, with a higher prevalence in males (APA, 2014). The disorder has a significant impact on the lives of children and their families (FRARE et al*.,* 2020)

One of the main objectives of the treatment is to enable people with ASD to participate actively and independently in daily activities. For the core symptoms of ASD, behavioral and educational interventions are recommended; while, for the control of other symptoms, such as aggressive behavior, drug interventions may be an option (SIGN, 2016).

Children with ASD require a multidisciplinary therapeutic approach, with a wide range of behavioral, emotional, and social attention. Although there is no cure for ASD, several therapeutic interventions have been developed and studied to improve the quality of life of people with the disorder (VIANA et al*.,* 2020).

In this context, it is essential to highlight the effectiveness and tolerability of these interventions. Among the main interventions, there are behavioral interventions, communication interventions, social skills interventions, pharmacological interventions, and complementary and alternative therapies (APA, 2014).

However, the efficacy and tolerability of interventions may vary according to the individual characteristics of each person with ASD, the stage of development, and the presence of comorbidities (FRARE et al*.,* 2020). In addition, the choice and implementation of therapeutic interventions is individualized, based on the specific needs and goals of each child, in addition to being supervised by specialized professionals (VIANA et al*.,* 2020).

Furthermore, the involvement and support of the family are fundamental for the success of the interventions. Continuous follow-up and adaptability to treatment are also important to ensure the efficacy and tolerability of therapeutic interventions in ASD (APA, 2014).

Among the therapeutic interventions, it is worth highlighting pharmacotherapy , in which in some cases, medications can be prescribed to treat specific symptoms associated with ASD, such as hyperactivity, anxiety, aggressiveness, or sleep problems. However, it is important to emphasize that medication is not a cure for ASD and it should be used with caution, under appropriate medical-pharmaceutical supervision (HODGES; FEALKO; SOARES, 2020).

Among the expected benefits of understanding pharmacotherapeutic treatment, for example, is knowing the efficacy and safety of risperidone, as a widely used treatment option in the ASD population. These include improved social functioning and interaction, communication and adaptive skills, as well as a reduction in the frequency and severity of dysfunctional or negative behaviors; and promotion of academic functioning and cognition (FRARE et al., 2020).

In this context, it is important to know the positive and negative effects of this drug, around an appropriate and safe approach, taking into account the potential benefits and risks associated with its use. In addition, knowing which compounds are present in risperidone and their relationship to therapeutic and adverse effects can provide an understanding of the mechanisms of action involved, contributing to the development of more effective and personalized pharmacotherapeutic approaches.

Considering that risperidone has numerous advantages as a choice of treatment for autism spectrum disorder, resulting in improvements in children's behavioral and social symptoms, the present study is justified by pointing to the evidence of risperidone, aimed at the treatment of associated symptoms or comorbidities of ASD. The information from the present study will be based on evidence available in the scientific literature on the use of risperidone in the treatment of ASD, aiming to improve the quality of life of children with ASD and guide therapeutic protocols.

METHODOLOGY

The present research is a bibliographic review, of a qualitative and descriptive nature. According to Bastos and Ferreira (2016), a literature review research aims to answer a problem, through the use of bibliographic material, studies and scientific analyses, in addition, it is said to be of the qualitative type, as it analyzes the phenomena through an approach about a comprehensive paradigm. That is, demonstrating aspects that are not always clearly manifested.

A qualitative approach in pharmacology studies obtains data on a given occurrence in the literature, presents them in an organized way, facilitating access to scientific information and content synthesis, so that it can be understood, analyzed, compared in different contexts, and taken as a basis for subsequent trials, whether preclinical or clinical (FIEIRAS et al. 2023).

The study assumed the descriptive type due to the need to describe the characteristics of the clinical efficacy and tolerability of risperidone in the treatment of autism spectrum disorder in children, based on the positive and adverse therapeutic effects reported in the literature. Thus, a literature review was carried out to support the reflections on the theme of this study.

The works consulted were published from 2019 to 2023, on the Capes Journal Portal, which has free access to the electronic database of interest, the *National Library of Medicine* (PubMed). Descriptors organized in Boolean logic according to the following semantic fields were used: "*Risperidone*" in association with "*in the Treatment of Autism Spectrum Disorder in Children*"; " Risperidone", in association with "in the treatment of autism spectrum disorder in children", in which a search key was performed for each associated term. In the scope of the search, the option "search all" was maintained, the descriptors should contain in the title of the work, the type of material considered "all", with language limitation (English or Portuguese).

The methodological basis used was the literature review by Fieiras *et al.* (2021), who evaluated the efficacy and safety of risperidone and aripiprazole in children with ASD, through an overview of systematic reviews on the subject. The data from the final group of articles were summarized in order to observe the advantages and disadvantages of the use of risperidone in childhood ASD.

RESULTS AND DISCUSSIONS

The search found 30 studies, 20 were open access and 10 were paid, only one article was published in Brazil, 24 were peer-reviewed and 06 were not. The research points to the scarce production of research on ASD associated with a treatment in children, such as risperidone. The articles considered for this study are shown in Table 1.

Table 1: Studies considered in this literature review

Year	Title	Authorship	Goal
2020	We Really Need Clear Guidelines and Recommendations for Safer and Proper Use of ripiprazole and Risperidone in a Pediatric Population: Real-World Analysis of EudraVigilance	Rafaniello *et al.*	To perform a comprehensive overview of adverse events reported among children and adolescents treated with aripiprazole and risperidone.
2020	Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with Autism spectrum disorder	Kloosterboer *et al*.	To assess the relationship between risperidone and 9-hydroxyrisperidone at trough concentrations, peak concentrations, and 24-hour area under the curves (AUCs) with body mass index (BMI) z-scores in children and adolescents with autism spectrum disorder (ASD) and behavioral problems.

2020	Olanzapine, risperidone, and aripiprazole use in children and adolescents with Autism Spectrum Disorders	Hesapcioglu *et al*.	To examine the use of olanzapine, risperidone, and aripiprazole in autism spectrum disorders (ASD) in terms of their effects and side effects.
2020	Risperidone Induced Obesity in Children and Adolescents With Autism Spectrum Disorder: Genetic and Clinical Risk Factors	Vanwong *et al*.	To compare the prevalence of overweight and obesity among children and adolescents with autism spectrum disorder (ASD) treated with risperidone with the general pediatric population. To investigate the association of HTR2C-759C>T, ABCB1 1236C>T, ABCB1 2677G>T/A and ABCB1 3435C>T polymorphisms with risperidone-induced overweight and obesity in children and adolescents with ASD.
2021	Comparing the Effect of Risperidone, Virtual Reality and Risperidone on Social Skills, and Behavioral Problems in Children with Autism: A Follow-up Randomized Clinical Trial	Kouhbanani *et al.*	Design a virtual reality (VR) intervention based on the TEACCH method in combination with risperidone to evaluate its effectiveness on social and behavioral problems.
2021	Effects of Risperidone in Autistic Children and Young Adults: A Systematic Review and Meta-Analysis	Sousa *et al.*	To investigate the effects of risperidone on five domains of the *Aberrant Behavior Checklist* (ABC) scale in Autism Spectrum Disorder (ASD), as well as weight gain and waist circumference.
2021	Body mass index increase in preschoolers with heterogeneous psychiatric diagnoses treated with risperidone	Avrahami *et al.*	To assess changes in body mass index (BMI) that are associated with risperidone treatment in preschool children.
2021	Risperidone or Aripiprazole Can Resolve Autism Core Signs and Symptoms in Young Children: Case Study	Alsayouf *et al*.	Suggest that ASD can potentially be treated in very young children (<4 years)
2022	Effectiveness and Adverse Effects of Risperidone in Children with Autism Spectrum Disorder in a Naturalistic Clinical Setting at a University Hospital in Oman	Al-Huseini *et al*.	To examine the effectiveness of treating children with autism spectrum disorder (ASD) who exhibit irritability, aggression, and disruptive behavior at Sultan Qaboos University Hospital (SQUH) in Muscat, Oman, with risperidone, and to note any sex-based differences among this cohort.
2022	Core Signs and Symptoms in Children with Autism Spectrum Disorder Improved after Starting Risperidone and Aripiprazole in Combination with Standard Supportive Therapies: A Large, Single-Center, Retrospective Case Series	Alsayouf; Stalk; Biddappa	To present a retrospective case series of 82 children aged 2 to 13 years with ASD and the associated behavioral comorbidities that were refractory to standard supportive therapies

Source: Author, 2025

Autism Spectrum Disorder is a neurodevelopmental disorder characterized by a series of symptoms that can affect social interaction, communication, and behavior. Children with ASD may have difficulties in social skills, repetitive behaviors, and varying degrees of cognitive impairment. Common behavioral problems include irritability, anger behavior, and aggression, which can significantly impact your daily functioning and quality of life (HESAPCIOGLU et al.,

2020).

ASD is heterogeneous, meaning each child with ASD presents unique challenges, and while some symptoms may improve with age, others may persist into adulthood, leading to poor social and emotional development outcomes. Some drugs used for the treatment of children, such as risperidone, reveal a picture of potential benefits and significant risks (ALSAYOUF et al., 2021).

The prevalence of ASD has led to increased attention on effective treatment options (KLOOSTERBOER et al., 2020). Standard treatment for ASD involves early intervention strategies, including behavioral, occupational, and speech therapies designed to support development and improve socialization. Currently, no drug is defined as the gold standard by regulatory agencies, specifically to treat the main symptoms of ASD. Instead, medications are often prescribed to manage comorbid symptoms such as irritability and aggression, particularly in older children (ALSAYOUF et al., 2021).

Risperidone, an atypical antipsychotic, is studied for its effectiveness in treating challenging behaviors associated with ASD. The study by Alsayouf *et al.* (2021) reports that treatment with risperidone leads to marked improvements in Clinical Global Impressions Improvement (CGI-I) scores, with complete resolution of ASD signs and symptoms seen in 60% of treated children.

Risperidone has been shown to significantly reduce irritability, aggression, and hyperactivity in children with ASD. Studies indicate that it can improve behavioral symptoms and facilitate better engagement in social interactions (KOUHBANANI et al., 2021). Early diagnosis and treatment are crucial to improve the prognosis of children with ASD. The high levels of synaptogenesis and synaptic pruning that occur in early childhood may make this period particularly responsive to pharmacological interventions (ALSAYOUF et al., 2021).

Administration of risperidone is associated with improvements in behavioral and social skills. Patients exhibit improved eye contact, social relationship, and reduction in aggressive and self-injurious behaviors. These improvements are critical, as they can significantly improve the quality of life of children with ASD and their families (ALSAYOUF et al., 2021).

While risperidone can significantly improve social skills, it can mitigate certain behavioral problems that allow children to participate more effectively in social situations. This is particularly relevant when combined with other interventions (KOUHBANANI et al., 2021). Clinical evidence from the study by Rafaniello et al. (2020) suggest that risperidone may lead to significant reductions in aggressive behaviors and improve overall functioning in children with ASD.

Although risperidone primarily targets behavioral symptoms, improvements in behavior

may indirectly support better social interactions and communication skills (RAFANIELLO et al., 2020). In the meantime, Sousa et al. (2021) describe risperidone treatment associated with a significant reduction in irritability, reporting improvements of up to 43% in mean change scores on the Aberrant Behavior Checklist (ABC). They also see improvement in hyperactivity and other behavioral symptoms, making it an option for managing severe behavioral problems in children with ASD.

Risperidone has been shown to reduce irritability and aggression in children with ASD, leading to improved behavior and social interactions. The study by Kloosterboer et al. (2020) found a significant association between higher plasma concentrations of risperidone and greater efficacy in reducing irritability, as measured by the Aberrant Behavior Checklist ($p < 0.01$), suggesting that there is a therapeutic window for risperidone, however, with careful monitoring of plasma levels to increase safety and efficacy in treatment.

Risperidone appears to be effective in reducing irritability, aggression, and self-injurious behaviors in children with ASD. Hesapcioglu et al. (2020) report that children treated with risperidone demonstrate improvements in behavioral problems, including decreased frequency of tantrums, reduced aggression towards others, improved social skills, according to the application of the Vineland Adaptive Behavior Scale (VABS).

Among the positive therapeutic effects of risperidone, supported by several studies, its efficacy has been shown in managing irritability and associated behavioral problems in patients with ASD. However, despite its benefits, risperidone is also reported to trigger several adverse effects, the most common of which comprise weight gain, sedation, increased sleep duration, possible metabolic changes (HESAPCIOGLU et al., 2020).

The studies by Vanwong et al. (2020) describe risperidone as improving behavioral symptoms (reduced aggression and irritability), with increased ability Reducing these disruptive behaviors facilitates better social engagement and communication skills, although the extent of these improvements varies between individuals.

Risperidone is described as an atypical antipsychotic for improving behavioral symptoms in children with ASD. In a retrospective case series involving 82 children aged 2 to 13 years, treatment with risperidone resulted in significant progress in major ASD symptoms and comorbid behaviors. Most participants demonstrated complete remission of symptoms, as measured by the *Clinical Global Impression* scale (ALSAYOUF; STALK; BIDDAPPA, 2022).

According to lsayouf, Talo and Biddappa (2022) also considered that the positive therapeutic effects of risperidone are based on a reduction in irritability, aggression and other disruptive behaviors. These improvements can facilitate better social interactions and increase

learning opportunities for children with ASD. Combining risperidone with ADHD medications, when needed, is suggested to provide additional support for attention and cognitive development, which are essential for effective learning.

In the conception of Al-Huseini et al. (2021), risperidone is effective in reducing irritability, aggression, and disruptive behaviors in children with ASD. The study reported that low-dose risperidone monotherapy is effective and well tolerated among children who exhibit disruptive behavior. Although risperidone's primary focus is on behavioral symptoms, improvements in social skills may also be seen as a secondary benefit of reduced irritability and aggression.

According to Alsayouf et al. (2021) warn that as much as the therapeutic effects of risperidone are positive, its use is not without risks. Many patients experience weight gain, sedation, and elevated prolactin levels. In the study by Alsayouf et al. (2021), 30% of patients experienced weight gain and 20% had asymptomatic elevated prolactin. Although most adverse effects were mild and manageable, they require careful monitoring and consideration of the overall treatment plan.

Common adverse effects of risperidone observed by Kouhbanani et al. (2021), include weight gain, metabolic disorders, and other physical health problems. These effects can be significant, leading to concerns about the long-term use of the drug. While Kouhbanani et al. (2021) reiterate that after discontinuation of risperidone, many children experience a relapse of behavioral symptoms, indicating that risperidone may not provide a lasting solution without ongoing treatment.

According to Rafaniello et al. (2020) state that amid the benefits of risperidone, this use is associated with several adverse effects, which are essential to be considered, for example, a significant proportion of events are reported in the literature, some cases requiring hospitalization. Among the common side effects, the authors listed weight gain, sedation, metabolic alterations, and extrapyramidal symptoms (movement disorders). The risk of these side effects requires careful monitoring and management by healthcare professionals.

One of the most significant concerns associated with the use of risperidone in children is weight gain, according to Avrahami et al. (2021). That study reported an association between risperidone treatment and increased body mass index (BMI), which raises concerns about long-term metabolic health, leading to other health problems such as diabetes and cardiovascular problems.

The findings of Avrahami et al. (2021) also suggest that female preschoolers may have a higher risk of weight gain related to antipsychotic treatment, requiring monitoring of risperidone use. While risperidone may help reduce certain disruptive behaviors, its effects on enhancing

social and communication skills are less clear. Although behavioral symptoms improve, risperidone does not significantly improve social interaction or communication skills (SOUSA et al., 2021).

For Sousa et al. (2021) also consider that even though there are numerous benefits, the use of risperidone is associated with several adverse effects, which have raised concerns, namely weight gain and metabolic problems, one of the most significant concerns is the potential for weight gain and the development of metabolic syndrome, which can lead to long-term health complications, such as type 2 diabetes mellitus. In addition to other common effects, including sedation, increased appetite, and hormonal changes, which can affect growth and development in children.

One of the most significant adverse effects reported is weight gain, which is more pronounced in children than in adults. This can lead to long-term health risks, including metabolic abnormalities and diabetes. Extrapyramidal symptoms (EPS) have also been reported, one in three children may experience mild to moderate EPS during treatment, which may include symptoms such as tremors and rigidity. More than half of children treated with risperidone may have elevated prolactin levels, potentially leading to gynecomastia and sexual dysfunction. Increased sedation is also reported in young patients, which can affect daily functioning and quality of life (KLOOSTERBOER et al., 2020).

According to Hesapcioglu et al. (2020), they point out that risperidone, even with a safety and efficacy profile, causes side effects, particularly weight gain, are significant considerations when prescribing this drug. The article emphasizes that the benefits of symptom control should be weighed against the potential for adverse effects, especially in the pediatric population.

A significant adverse effect reported in the study by Vanwong et al. (2020) is weight gain, with a notable prevalence of overweight and obesity (including insulin resistance), which may further complicate the health profile of children with ASD treated with risperidone. This raises concerns about the long-term health implications for these children. In addition, side effects of sedation, fatigue, and extrapyramidal symptoms are observed, which can affect the child's overall well-being.

Despite the positive results, according to Isayouf, Talo and Biddappa (2022), the use of Risperidone is not without risks. Common adverse effects reported include drowsiness, excessive salivation, weight gain, and asymptomatic elevated prolactin levels. The study noted that while some side effects were manageable or transient, the potential for significant adverse effects needs careful monitoring, especially considering that these medications are often prescribed *off-label* to younger children, hence the importance of considering each child's

individual age and circumstances when prescribing risperidone.

Finally, Al-Huseini et al. (2021) also adds that one of the most concerning side effects reported in the literature is significant weight gain, which can have long-term health implications, increased sleepiness or sedation is also observed as a common side effect, some children have movement disorders associated with medication (extrapyramidal symptoms), others have elevated prolactin levels, warranting careful monitoring and consideration when prescribing risperidone.

CONCLUSION

This literature review analyzes the clinical efficacy and tolerability of risperidone in the treatment of Autism Spectrum Disorder (ASD) in children. The reviewed studies demonstrate that risperidone can be effective in reducing behavioral symptoms, such as irritability, aggressiveness, and disruptive behaviors, contributing to better social and functional adaptation of patients.

In addition, the results reinforce that medication can be a viable alternative for children with ASD who have significant difficulties in behavioral management.

However, the benefits of risperidone must be weighed against its adverse effects, such as weight gain, sedation, and metabolic changes, all of which disable continuous monitoring. Although medication has shown positive results, it should not be considered as the only therapeutic approach, but rather integrated with multidisciplinary strategies, including behavioral and educational interventions.

Thus, it is essential that future research broadens the scope of investigations on the use of risperidone in children with ASD, especially in relation to the long-term effects and the development of more precise clinical guidelines for its administration. In addition, studies evaluating combined therapeutic alternatives can contribute to a more individualized and effective treatment.

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