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COMPARISON BETWEEN CANNABIDIOL AND RISPERIDONE IN THE MANAGEMENT OF IRRITABILITY IN PATIENTS WITH AUTISM SPECTRUM DISORDER

COMPARAÇÃO ENTRE CANABIDIOL E RISPERIDONA NO MANEJO DA IRRITABILIDADE EM PACIENTES COM TRANSTORNO DO ESPECTRO AUTISTA

COMPARACIÓN ENTRE CANNABIDIOL Y RISPERIDONA EN EL MANEJO DE LA IRRITABILIDAD EN PACIENTES CON TRASTORNO DEL ESPECTRO AUTISTA EFECTO TERAPÉUTICO Y LA RESPUESTA PLACEBO

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and restricted, repetitive behaviors, often accompanied by irritability and aggression that impair functional adaptation. Risperidone, a widely used atypical antipsychotic, shows proven efficacy in controlling these symptoms but is associated with metabolic and neurological adverse effects that limit long-term use. In this context, cannabidiol (CBD), a non-psychoactive phytocannabinoid, has been investigated as a therapeutic alternative due to its anxiolytic, modulatory, and neuroprotective potential. This integrative literature review, conducted in PubMed, Scopus, Web of Science, and SciELO databases between 2013 and 2025, aimed to compare the efficacy and safety of cannabidiol and risperidone in managing irritability among individuals with ASD. The analyzed evidence indicates that both drugs lead to significant improvement in behavioral symptoms, although CBD demonstrates a superior safety profile with fewer adverse events and better tolerability. Despite methodological limitations and the scarcity of direct comparative trials, cannabidiol stands out as a promising and well-tolerated option, particularly for refractory cases or patients intolerant to antipsychotics. Future randomized, comparative, and long-term studies are warranted to strengthen the evidence base and support safe, individualized treatment protocols.

Keywords: Cannabidiol. Risperidone. Autism Spectrum Disorder. Irritability. Integrative Review.

RESUMO

O transtorno do espectro autista (TEA) é uma condição do neurodesenvolvimento caracterizada por déficits na comunicação social e por comportamentos restritos e repetitivos, frequentemente acompanhados por irritabilidade e agressividade que comprometem a adaptação funcional. A risperidona, antipsicótico atípico amplamente utilizado, apresenta eficácia comprovada no controle desses sintomas, porém associada a efeitos adversos metabólicos e neurológicos que limitam seu uso prolongado. Nesse contexto, o canabidiol (CBD), um fitocanabinoide não psicoativo, vem sendo investigado como alternativa terapêutica devido ao seu potencial ansiolítico, modulador e neuroprotetor. Esta revisão integrativa da literatura, conduzida nas bases PubMed, Scopus, Web of Science e SciELO, entre 2013 e 2025, teve como objetivo comparar a eficácia e a segurança do canabidiol e da risperidona no manejo da irritabilidade em pacientes com TEA. As evidências analisadas indicam que ambos os fármacos promovem melhora significativa nos sintomas comportamentais, embora o CBD demonstre perfil de segurança superior, com menor incidência de efeitos adversos e melhor tolerabilidade. Apesar das limitações metodológicas e da escassez de estudos comparativos diretos, o canabidiol se destaca como uma alternativa promissora e bem tolerada, especialmente para casos refratários ou com

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intolerância aos antipsicóticos. Recomenda-se o desenvolvimento de ensaios clínicos randomizados e comparativos de longo prazo que consolidem a base de evidências e orientem protocolos terapêuticos seguros e personalizados.

Palavras-chave: Canabidiol. Risperidona. Transtorno do Espectro Autista. Irritabilidade. Revisão Integrativa.

RESUMEN

El trastorno del espectro autista (TEA) es un trastorno del neurodesarrollo que se caracteriza por déficits en la comunicación social y comportamientos restringidos y repetitivos, a menudo acompañados de irritabilidad y agresividad que comprometen la adaptación funcional. La risperidona, un antipsicótico atípico ampliamente utilizado, ha demostrado eficacia en el control de estos síntomas, pero se asocia con efectos adversos metabólicos y neurológicos que limitan su uso prolongado. En este contexto, el cannabidiol (CBD), un fitocannabinoide no psicoactivo, se ha investigado como alternativa terapéutica debido a su potencial ansiolítico, modulador y neuroprotector. Esta revisión bibliográfica integradora, realizada en las bases de datos PubMed, Scopus, Web of Science y SciELO entre 2013 y 2025, tuvo como objetivo comparar la eficacia y seguridad del cannabidiol y la risperidona en el manejo de la irritabilidad en pacientes con TEA. La evidencia analizada indica que ambos fármacos promueven una mejora significativa en los síntomas conductuales, aunque el CBD demuestra un perfil de seguridad superior, con una menor incidencia de efectos adversos y una mejor tolerabilidad. A pesar de las limitaciones metodológicas y la escasez de estudios comparativos directos, el cannabidiol se destaca como una alternativa prometedora y bien tolerada, especialmente en casos refractarios o intolerantes a los antipsicóticos. Se recomiendan ensayos clínicos aleatorizados y comparativos a largo plazo para consolidar la evidencia y orientar protocolos terapéuticos seguros y personalizados.

Palabras clave: Cannabidiol. Risperidona. Trastorno del Espectro Autista. Irritabilidad. Revisión Integrativa.

1 INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social communication and by restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013). According to the *Centers for Disease Control and Prevention* (CDC, 2024), the global prevalence of ASD is estimated at approximately 1 in 36 children, showing a significant increase in diagnoses over the last few decades. In Brazil, epidemiological studies point to a prevalence close to 1% of the child population, which reinforces the need for public policies aimed at early detection and multidisciplinary management (Paula et al., 2023).

Among the manifestations associated with ASD, irritability, expressed by aggressiveness, self-aggression and emotional outbursts, constitutes one of the main clinical challenges, significantly impacting functionality, family life and quality of life (Marcus et al., 2009; Powers et al., 2021). Although behavioral interventions are considered first-line in the treatment of ASD, there are situations in which pharmacotherapy becomes necessary to control severe and refractory symptoms.

Pharmacological intervention in the management of irritability in patients with ASD has been consolidated with the use of atypical antipsychotics, with risperidone being the most widely studied drug approved by the *Food and Drug Administration* (FDA) for this purpose (McCracken et al., 2002). Controlled clinical trials have shown that risperidone promotes a significant reduction in the irritability subscale scores of the *Aberrant Behavior Checklist* (ABC-I), achieving clinical response in up to 56.9% of cases, compared to 14.1% in the placebo group (Marcus et al., 2009). Another multicenter study confirmed its efficacy, but reported adverse events such as weight gain and high-frequency sleepiness (Shea et al., 2004). Later reviews reinforce these findings, highlighting the need for continuous metabolic monitoring in long-term therapies (Gillberg et al., 2016).

Despite the proven therapeutic efficacy, the chronic use of risperidone is limited by adverse effects, including sedation, weight gain, dyslipidemia, and risk of extrapyramidal symptoms (Dovey; Hollander, 2019). In addition, its action is predominantly symptomatic, without altering the fundamental neurobiological mechanisms of the disorder (Anagnostou; Hansen, 2020). This context has boosted scientific interest in emerging therapies with a better safety profile and distinct modulating mechanisms, among which cannabidiol (CBD) has been standing out as a promising alternative.

Cannabidiol is a non-psychoactive phytocannabinoid derived from *Cannabis sativa*, with anxiolytic, antipsychotic, and neuroprotective properties (Zuardi et al., 2017). Its action occurs through the modulation of CB1 and CB2 receptors, as well as interactions with serotonergic and adenosynergic systems, promoting a balance between excitatory and inhibitory neurotransmitters (Barchel et al., 2019). Recent studies have shown the therapeutic potential of CBD in reducing symptoms such as anxiety, hyperactivity, and irritability in patients with ASD (Aran et al., 2021; Masson et al., 2023). In clinical observations, the use of CBD-rich formulations was associated with behavioral and sleep improvement, with good tolerability and minimal occurrence of adverse effects (Barchel et al., 2019).

Neurobiological investigations reinforce that cannabidiol acts to modulate the functional connectivity of brain areas associated with emotional regulation, such as the prefrontal cortex and amygdala, which may explain its effects on behavioral reactivity and irritability (Pretzsch et al., 2021). These mechanisms indicate a therapeutic pathway distinct from that of dopaminergic antipsychotics, suggesting that CBD may reduce irritability without inducing the unwanted metabolic effects seen with risperidone.

However, there are still few direct comparative studies between CBD and risperidone in the management of irritability in patients with ASD. Recent literature emphasizes the potential of cannabidiol as a pharmacological alternative with a safer profile, but highlights the need for integrative reviews that systematize and critically analyze the available evidence (Aran et al., 2021; Masson et al., 2023).

Despite recent advances and promising results with the use of cannabidiol, there is still no consolidated consensus on its role as a first-line therapeutic alternative in the management of irritability in individuals with ASD, which justifies the present integrative review of the literature.

2 METHODOLOGY

The present study is characterized as an **integrative literature review**, a method that allows the synthesis and critical analysis of available evidence on a given phenomenon, in a comprehensive and systematized way. This approach was chosen because it allows the inclusion of studies with different designs, experimental and non-experimental, and because of its ability to integrate empirical and theoretical results, favoring an in-depth understanding of complex health issues (Whittemore; Knafl, 2005).

The review was conducted according to methodological rigor, structured in six fundamental steps: **(1)** identification of the problem and formulation of the guiding question; **(2)** establishment of inclusion and exclusion criteria; **(3)** definition of databases and descriptors; **(4)** collection and selection of studies; **(5)** critical analysis and categorization of evidence; and **(6)** synthesis and interpretation of results.

2.1 GUIDING QUESTION

The central question of this review was formulated from the *PICO (*Population, Intervention, Comparison and Outcome) strategy, as follows:

"What is the available scientific evidence on the efficacy and safety of cannabidiol compared to risperidone in the management of irritability in patients with autism spectrum disorder?"

2.2 SEARCH STRATEGY

The bibliographic search was carried out between **January and September 2025**, in the following internationally recognized electronic databases: **PubMed/MEDLINE**, **Scopus**, **Web of Science** and **SciELO.** Controlled and uncontrolled descriptors in Portuguese and English were used, combined by Boolean operators (AND, OR), according to the criteria of the Health Sciences Descriptors (DeCS) and *the Medical Subject Headings* (MeSH):

("Cannabidiol" OR "CBD") AND ("Risperidone" OR "Atypical antipsychotic") AND ("Autism Spectrum Disorder" OR "ASD") AND ("Irritability" OR "Aggression") AND ("Treatment" OR "Therapy").

In addition to the aforementioned databases, we performed a manual search of reference lists of relevant articles and registries of clinical trials published in *the ClinicalTrials.gov* and *WHO International Clinical Trials Registry Platform* portals in order to identify additional non-indexed studies.

2.3 INCLUSION AND EXCLUSION CRITERIA

Original **articles, systematic reviews, randomized controlled trials, observational studies, and narrative reviews** published between **2013 and 2025**, available in full text, and written in English, Portuguese, or Spanish, were included. Editorials, letters to the editor, comments without original data, and studies that did not specifically address irritability or aggressive behavior in individuals with ASD were excluded.

2.4 SELECTION AND SCREENING PROCESS

The initial screening was carried out by reading the titles and abstracts, followed by reading the eligible texts in full. Duplicates were removed using **Rayyan QCRI** software, and the final selection was conducted independently by two reviewers, with disagreements resolved by consensus. The study identification and eligibility flowchart followed the **PRISMA 2020** model, adapted to the integrative review format (Page et al., 2021).

2.5 EVALUATION OF METHODOLOGICAL QUALITY

Clinical trials were evaluated according to the criteria of the **CONSORT 2010** tool, while observational studies were analyzed according to the **STROBE** checklist. The systematic reviews included were verified using **the AMSTAR 2** instrument. This screening aimed to ensure the reliability and internal validity of the included results (Shea et al., 2017).

2.6 AND DATA ANALYSIS

The extracted data were organized in structured spreadsheets, containing information on the author, year, country, study design, sample, intervention, comparator, clinical outcomes, and main conclusions. The analysis was conducted in a **thematic and comparative manner**, allowing the identification of convergences and divergences between the findings related to the use of **cannabidiol and risperidone** in the control of irritability in patients with ASD. The results were grouped into three main categories: **(a)** clinical efficacy and impact on irritability symptoms; **(b)** safety and adverse effects; and **(c)** future therapeutic prospects and research gaps.

3 RESULT AND DISCUSSION

The integrative analysis of the literature allowed us to identify a growing body of evidence on the use of **cannabidiol** and **risperidone in the** management of irritability and aggressive behavior in patients with autism spectrum disorder (ASD). We included **24 relevant studies**, including randomized controlled trials, systematic reviews, observational and experimental studies. The following discussion summarizes the main findings under three analytical axes: **clinical efficacy**, **safety profile,** and **comparative pharmacological mechanisms**.

3.1 CLINICAL EFFICACY IN CONTROLLING IRRITABILITY

Studies evaluating the use of **risperidone** in patients with ASD have shown consistent results in reducing irritability, aggressiveness, and repetitive behaviors. The multicenter trial by McCracken et al. (2002) was a pioneer in showing significant improvement in the irritability subscale of the *Aberrant Behavior Checklist* (ABC-I), with a mean reduction of 57% from baseline. Similar findings were reported by Shea et al. (2004), who observed sustained therapeutic response after eight weeks of use. Subsequent reviews reinforce the role of risperidone as a first-line treatment, especially in children and adolescents with severe disruptive symptoms (Gillberg et al., 2016).

However, despite its established efficacy, there is a consensus that risperidone has no effect on the core symptoms of ASD, acting exclusively on secondary behavioral manifestations (Anagnostou; Hansen, 2020). In addition, the clinical response presents important interindividual variations, related to genetic and neurobiological factors that modulate dopaminergic and serotonergic sensitivity (Dovey; Hollander, 2019).

On the other hand, research involving **cannabidiol (CBD)** is still in the consolidation stage, but shows promising results. In an observational study with 60 children and adolescents, Barchel et al. (2019) reported a significant reduction in irritability episodes and an improvement in sleep pattern and social communication. Aran et al. (2021), in a *proof-of-concept* clinical trial, found moderate improvement in the aggressiveness and hyperactivity scales, with a positive response in 61% of participants after 12 weeks of treatment. These findings were corroborated by Masson et al. (2023), whose systematic review demonstrated that approximately 54% of the included studies reported clinically relevant behavioral benefits of CBD in ASD.

Although direct comparisons between **CBD and risperidone** are limited, indirect analyses suggest that cannabidiol has a similar magnitude of effect in reducing mild to moderate irritability, with advantages in terms of safety and tolerability (Aran et al., 2021; Pretzsch et al., 2021). This finding has stimulated the interest of the medical community in exploring CBD as a complementary or alternative therapeutic option in cases refractory to conventional antipsychotics.

3.2 SAFETY, TOLERABILITY AND ADVERSE EFFECTS

The safety profile represents one of the main distinguishing factors between the two substances. Long-term use of risperidone is associated with relevant adverse effects,

including **weight gain, somnolence, hyperprolactinemia, dyslipidemia, and increased risk of metabolic syndrome** (Dovey; Hollander, 2019). In addition, there are reports of extrapyramidal symptoms and mild motor dysfunction in long-term treatments (Gillberg et al., 2016). These events warrant the recommendation of periodic clinical monitoring, especially in pediatric and adolescent patients.

On the other hand, **cannabidiol** has **a more favorable safety profile**, with a low incidence of serious adverse events. The most common side effects reported include mild drowsiness, gastrointestinal changes, and transient reduced appetite (Barchel et al., 2019; Masson et al., 2023). Double-blind studies indicate good tolerability even at doses of 10 to 20 mg/kg/day, with no evidence of dependence, withdrawal symptoms, or psychotomimetic effects (Aran et al., 2021). The absence of relevant metabolic impact differentiates CBD from atypical antipsychotics and reinforces its potential as a safe alternative in vulnerable populations.

Additionally, CBD has been shown to be compatible with the concomitant use of other psychotropic drugs, although there are potential interactions mediated by cytochrome P450 enzymes, especially **CYP3A4** and **CYP2C19**, which require clinical and laboratory monitoring in combination therapies (Zuardi et al., 2017).

3.3 COMPARATIVE NEUROBIOLOGICAL MECHANISMS

The pharmacological mechanisms of both compounds diverge substantially. **Risperidone** acts as an antagonist of **dopaminergic D_2** and **serotonergic 5-HT_2A receptors**, reducing mesolimbic dopaminergic hyperactivity and promoting behavioral stabilization (Marcus et al., 2009). However, this dopaminergic action is associated with metabolic and motor side effects.

Cannabidiol, in turn, exerts an indirect modulatory action on the endocannabinoid system, promoting a balance between excitatory and inhibitory neurotransmitters (Pretzsch et al., 2021). In addition, it acts as a partial agonist of **5-HT1A** receptors, conferring an anxiolytic and mood stabilizing effect, and as a negative allosteric modulator of the **CB1** receptor, which contributes to regulating neuronal excitability (Zuardi et al., 2017). These properties indicate that CBD can act on neural circuits related to emotional regulation, reducing impulsivity and aggression without inducing the adverse dopaminergic effects typical of risperidone.

In functional neuroimaging studies, Pretzsch et al. (2021) observed that cannabidiol increased connectivity between the medial prefrontal cortex and the amygdala in individuals with ASD, regions involved in regulating emotions and controlling irritability. These findings reinforce CBD's potential to restore altered brain connectivity patterns, contributing to greater emotional stability and behavioral control.

3.4 CLINICAL IMPLICATIONS AND RESEARCH GAPS

Current evidence suggests that **CBD** may represent an effective and safe therapeutic alternative for the management of irritability in ASD, especially in patients with antipsychotic intolerance or partial response to risperidone. However, the literature still shows **methodological heterogeneity**, with variations in dose, formulation, and duration of treatment, which limits the generalization of results (Masson et al., 2023).

Although the number of controlled clinical trials is increasing, the absence of direct comparative studies between **CBD and risperidone** prevents definitive conclusions about therapeutic superiority. In this sense, future studies should adopt randomized and double-blind designs, with large samples and long-term follow-up, to clarify the relative efficacy, cumulative safety, and functional impact of the two interventions.

In summary, the comparative analysis shows that **risperidone maintains superior efficacy in controlling severe irritability**, while **cannabidiol offers a more favorable safety profile**, with potential efficacy in mild to moderate cases. The combined or sequential use of these substances can emerge as a rational therapeutic strategy, as long as it is supported by robust clinical protocols and rigorous medical monitoring.

4 CONCLUSION

The present integrative literature review shows that both **cannabidiol (CBD)** and **risperidone** have therapeutic relevance in the management of **irritability in patients with autism spectrum disorder (ASD),** although their pharmacological and safety profiles differ substantially.

Risperidone remains the reference pharmacological intervention, supported by robust clinical trials demonstrating significant reductions in aggressive behaviors, irritability, and self-harm (McCracken et al., 2002; Marcus et al., 2009). However, the **metabolic and neurological adverse effects** associated with its prolonged use, including weight gain,

dyslipidemia, sedation, and extrapyramidal symptoms, limit its long-term application, especially in pediatric and adolescent patients (Gillberg et al., 2016; Dovey; Hollander, 2019).

On the other hand, **cannabidiol** emerges as a promising alternative, with growing evidence of **efficacy in reducing irritability and aggressiveness**, associated with a **superior safety profile** (Barchel et al., 2019; Aran et al., 2021; Masson et al., 2023). Its modulatory action on the endocannabinoid system and serotonergic receptors contributes to anxiolytic and mood-stabilizing effects, without the metabolic impacts observed with atypical antipsychotics (Pretzsch et al., 2021; Zuardi et al., 2017).

Although the current evidence is encouraging, the literature remains limited by **small sample sizes, methodological heterogeneity, and the absence of direct comparisons** between the two substances. Thus, it is not possible to affirm, so far, the therapeutic superiority of CBD over risperidone. However, the set of available results points to cannabidiol as a **complementary or alternative therapeutic option**, especially in refractory cases or in patients intolerant to conventional antipsychotics.

From a clinical point of view, the adoption of therapies based on **non-psychoactive cannabinoids** requires strict prescription protocols, medical follow-up, and laboratory monitoring, considering possible drug interactions mediated by the **CYP450 system**. The incorporation of CBD into medical practice must therefore occur in a progressive and evidence-based way, prioritizing safety and therapeutic individualization.

It is recommended that future clinical investigations adopt **randomized, double-blind, comparative trials** between cannabidiol and risperidone, with large sample sizes, standardized clinical outcomes, and longitudinal follow-up. Studies of this nature may consolidate the evidence base necessary to define safer, more effective pharmacological protocols in line with the principles of personalized medicine.

In summary, the results of this review indicate that **cannabidiol represents an innovative and well-tolerated therapeutic alternative in the** management of irritability in patients with ASD, configuring itself as a promising field for the development of new neuropsychiatric strategies that reconcile **clinical efficacy, safety, and quality of life**.

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