

Use of Cannabidiol in Autism Spectrum Disorder: Evidence and Therapeutic Perspectives

Uso do Canabidiol no Transtorno do Espectro Autista: Evidências e Perspectivas Terapêuticas

Uso del Cannabidiol en el Trastorno del Espectro Autista: Evidencia y Perspectivas Terapéuticas

RESUMO

Objetivo: O presente artigo visa evidenciar os resultados obtidos por meio de estudos clínicos no gerenciamento das manifestações clínicas em pacientes com autismo. **Métodos:** Revisão integrativa de literatura. Foram usadas três bases de dados: PubMed, LILACS e Scielo. **Resultados:** O tratamento combinado de canabidiol demonstrou melhores resultados em vários aspectos em relação às manifestações do transtorno que afetam a qualidade de vida do portador. Apesar dos ótimos resultados, efeitos colaterais apareceram como aumento ou falta de apetite, insônia ou sonolência, diarreia e irritabilidade. **Conclusão:** Os achados sugerem que o uso de canabidiol pode ser uma abordagem promissora para o manejo de sintomas do autismo, com perfil de segurança relativamente favorável. No entanto, estudos de longo prazo são necessários para validar sua eficácia e segurança.

DESCRIPTORES: Transtorno Autístico; Transtorno do Espectro Autista; Canabidiol; Tratamento Farmacológico; Cannabis.

ABSTRACT

Objective: This article aims to highlight the results obtained through clinical studies in the management of clinical manifestations in patients with autism. **Methods:** Integrative literature review. Three databases were used: PubMed, LILACS, and SciELO. **Results:** Combined cannabidiol treatment demonstrated better results in several aspects related to the manifestations of the disorder that affect the quality of life of the individual. Despite the excellent results, side effects appeared such as increased or decreased appetite, insomnia or drowsiness, diarrhea, and irritability. **Conclusion:** The findings suggest that the use of cannabidiol may be a promising approach for managing autism symptoms, with a relatively favorable safety profile. However, long-term studies are needed to validate its efficacy and safety.

DESCRIPTORS: Autism Spectrum Disorder; Autistic Disorder; Cannabidiol; Drug Therapy; Cannabis.

RESUMEN

Objetivo: Este artículo busca destacar los resultados obtenidos a través de estudios clínicos en el manejo de las manifestaciones clínicas en pacientes con autismo. **Métodos:** Revisión bibliográfica integradora. Se utilizaron tres bases de datos: PubMed, LILACS y SciELO. **Resultados:** El tratamiento combinado con cannabidiol demostró mejores resultados en varios aspectos relacionados con las manifestaciones del trastorno que afectan la calidad de vida del individuo. A pesar de los excelentes resultados, aparecieron efectos secundarios como aumento o disminución del apetito, insomnio o somnolencia, diarrea e irritabilidad. **Conclusión:** Los hallazgos sugieren que el uso de cannabidiol puede ser un enfoque prometedor para el manejo de los síntomas del autismo, con un perfil de seguridad relativamente favorable. Sin embargo, se necesitan estudios a largo plazo para validar su eficacia y seguridad.

DESCRIPTORS: Autism Spectrum Disorder; Autistic Disorder; Cannabidiol; Drug Therapy; Cannabis.

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INTRODUCTION

Autism Spectrum Disorder (DSM-5 6A02 / ICD-11) is characterized by persistent deficits in social interaction and communication skills, along with inflexibility regarding patterns of behavior. In addition to the core symptoms, the disorder is often accompanied by psychiatric comorbidities such as epilepsy, depression, anxiety, and schizophrenia.^[1]

The manifestations of ASD can cause significant impairments in both the social and professional aspects of the individual's life. Depending on the severity of the condition, individuals may exhibit language deficits ranging from reduced comprehension to a complete absence of speech, as well as deficits in social-emotional reciprocity and nonverbal communication behaviors, such as a lack of eye contact during social interactions. Repetitive behaviors are also observed, such as motor stereotypies, recurrent use of objects, and repetition of speech.^[2]

According to the World Health Organization (WHO), it was estimated in 2022 that 1 in every 100 children worldwide has ASD^[3]. Although many of the symptoms are detectable during childhood, most diagnoses are made late^[4].

Despite its high prevalence, there is no specific treatment for managing the clinical manifestations. However, some symptoms can be alleviated through psychiatric medications combined with alternative therapies such as music therapy^[5], cognitive behavioral therapy (CBT)^[6], animal-assisted therapy^[7], etc.

In this regard, in 2020, the UN Commission on Narcotic Drugs removed cannabis from its most restrictive list, no longer classifying it as a drug with high potential for harm and thereby opening up new therapeutic opportunities^[8]. Cannabis sativa contains various compounds, including delta-9-THC (THC), a substance with psychoactive effects, and cannabidiol (CBD), whose use is associated with pharmaceutical properties^[9].

In this context, one of the emerging treatment approaches is the incorporation of cannabidiol into the therapeutic management of ASD. CBD modulates brain activity by activating the endocannabinoid system, which has antitumor and anxiolytic effects, among others. One of its effects is the reduction of limbic system activity and, consequently, a decrease in anxiety levels^[10]. Randomized studies have also demonstrated an improvement in psychomotor agitation and social interactions in individuals with socialization difficulties during CBD use^[11,12].

METHODOLOGY

Methodology Used

An integrative literature review was conducted to analyze and summarize information related to the use of cannabidiol (CBD) in the treatment of clinical manifestations of Autism Spectrum Disorder (ASD).

Identification of Studies

Three databases were used for the search: PubMed, LILACS, and Scielo. The searches included terms in Portuguese and English, using the subject

descriptor translator on the BVS Regional Portal, for the terms "Autistic Disorder," "Autism Spectrum Disorder," "Cannabidiol," "Pharmacological Treatment," and "Cannabis." The logical operators "AND" and "OR" were used in conjunction with the terms "subject descriptor" and "abstract."

Eligibility Criteria

The criteria for selecting eligible articles were established to ensure a qualitative study focused on the individual's progression as a patient and the presentation of data in an understandable manner. For inclusion, studies had to meet the following criteria:

- **Publication:** studies published between 2019 and 2024, in order to address topics in a more up-to-date and less conservative manner.
- **Data:** Studies that included tables and comprehensive information regarding sample size, age, treatment duration, and data related to changes in ASD symptoms.
- **Country of publication:** Studies from at least two different countries were selected to assess the influence of ethnocultural factors, as these are more relevant to treatment success.
- **CBD and THC:** Only studies involving the use of CBD in combination with THC were selected, as this is a more widely studied topic.
- **Autism Spectrum Disorder (ASD):** Studies focusing exclusively on ASD treatment were selected.

Exclusion Criteria

However, exclusion criteria were established to make the research more

specific, avoiding topics that diverged from the main theme. The exclusion criteria included:

- Animals: Any clinical trials conducted on animals were excluded, as human physiology differs from that of other species and results may not be applicable to humans.
- Year of publication: Studies published prior to 2018 were not included in the article because they

provided outdated information on the subject.

- Lack of data: Studies conducted on test subjects that lacked data interpretation, percentages, or detailed specifications of which symptoms were affected were ultimately excluded.
- Study Type: Systematic reviews, meta-analyses, and non-original studies (such as opinion pieces, let-

ters to the editor, and conference abstracts).

RESULTS

Of the 35 articles found, only 6 were selected because they addressed the topic in an up-to-date and accurate manner. Figure 1 shows the publication findings for each database portal used.

Figure 1. Comparative table of the publication findings from each database.			
Portais	PubMed	LILACS	SciELO
Número total	12	19	4
Filtragem	6	1	1
Seleção*	6		

*Duplicate records removed across databases.

After filtering, the studies were categorized by (1) author and year of publication, (2) methodology used, (3) sample size and mean age of participants, and (4) main research findings.

Figure 2: Analysis of the articles identified by author and year of publication; methodology; number of participants and mean age; main findings			
AUTHOR / YEAR OF PUBLICATION	METHODOLOGY	SAMPLE SIZE / AVERAGE AGE / DURATION	MAIN FINDINGS
Silva Junior et al, 2024 ^[13]	Randomized	60 participants Age: 11 years 12 weeks	Improvement in aggression (41%), anxiety (37%), concentration (42%), socialization (40%), and speech (23%) Adverse effects: loss of appetite and insomnia
Barchel et al, 2019 ^[14]	Prospective cohort	53 participants Age: 11 years 30 days	Improvement in hyperactivity (68.4%); in self-harm (67.6%); in sleep disorders (71.4%); and in anxiety (47.1%). Adverse effects: Drowsiness (22.6%), loss of appetite (11.3%).
FleuryTeixeira et al 2019 (scielo) ^[15]	Prospective cohort	18 participants Age: 10.9 years 9 months	Improvement in frequency of epileptic seizures (50%); ADHD (30%); social interaction (25%); behavioral disorders (20%); motor deficits (20%); cognitive deficits (20%) Adverse effects: Drowsiness, irritability, diarrhea, increased appetite, conjunctival hyperemia

Siani-Rose, 2023 ^[16]	Retrospective observational	24 participants Age: 9 years 1 year	Improvement in emotional regulation (86.7%), behavior (86.7), attention (92%), and repetitive movements (73%)
Schleider et al 2019 ^[17]	Retrospective observational	188 participants Age: 12 years 2 years	Improvement in aggression (43.3%), agitation (38.5%), anxiety (34.8%), seizures (47%), and sleep disturbances (23.9%) Adverse effects: drowsiness (3.2%), relaxation (6.6%), loss of appetite (2.2%)
Mazza et al, 2024 ^[18]	Retrospective observational study	30 participants Age: 11.5 years 6 months	Improvements in communication and learning (47%), affectivity (43%), aggression and irritability (60%), agitation (40%), self-harm (43%), increased appetite (30%), insomnia (33%), and repetitive speech (27%) Adverse effects: worsening of affect, irritability, agitation, insomnia, and increased appetite in 3% of cases

The studies analyzed were conducted in countries such as Brazil (3), Israel (2), and the United States (1). Collectively, the studies included participants aged 3 to 25 years; however, most researchers chose to include participants aged 5 years and older—who are still in the process of cognitive development—in order to ensure a more accurate and consistent neuropsychological assessment^[11]. Despite the young age of the participants, the number of individuals ranged from 18 to 188, with clinical treatments lasting more than one year.

Most researchers did not differentiate their studies based on the severity of autism, which ranged from mild to severe. For admission to their respective screening processes, participants took standardized tests to assess their verbal and mental cognition and their autism spectrum status, including both the *Childhood Autism Rating Scale* (CARS) and the *Wechsler Scale* (WISC-IV or WASI).

The combined treatment of CBD and THC demonstrated better results in several aspects related to ASD symptoms. Overall, there was an improvement in aggression, hyperactivity, anxiety, communication, concentration, socialization, self-injury, sleep disturbances, repetitive movements, seizures, epileptic episodes, and increased appetite. The improvements mentioned are all encompassed within the areas of cognitive and verbal enhancement. Despite the excellent results, side effects included increased or decreased appetite, insomnia or

drowsiness, diarrhea, and irritability.

DISCUSSION

Autism Spectrum Disorder

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), Autism Spectrum Disorder (ASD) is characterized by (1) persistent deficits in social communication and social interaction across multiple contexts; (2) Restricted and repetitive patterns of behavior, interests, or activities; (3) Symptoms present early in development; (4) Symptoms cause clinically significant impairment in social, occupational, or other important areas of the individual's life at present; and (5) Is no longer attributable to manifestations of intellectual disability.^[1]

Deficits in communication, social interaction, and repetitive and restrictive patterns of behavior.

Deficits in social skills are a major diagnostic factor. Their severity is categorized into three levels: the first requiring some support, the second requiring substantial support, and the third requiring very substantial support.

At Level 1, regarding social communication, the patient has difficulty initiating or maintaining social interactions, responding only to direct approaches. Regarding repetitive behaviors, there is inflexibility and difficulty changing routines.

At Level 2, in terms of socialization, there is impaired verbal and non-

verbal communication—even with support—and an abnormal response to social overtures. Inflexibility and difficulty changing behavior also cause distress to the individual.

Finally, at Level 3, in the absence of support, there is significant difficulty initiating social interactions, resulting in atypical responses or no success at all in responding to initial overtures from others. The patient's behavior and its inflexibility lead to difficulty organizing and planning daily tasks.

Interpersonal Relationships

As discussed earlier, patients with ASD tend to have greater difficulty with social interactions, which hinders not only their friendships but also their professional and romantic lives^[19]. Access to social and emotional relationships can be a challenge, as they involve social interpretation and sensory issues, which often end up being an obstacle for the individual. In the workplace, the challenges are significant, not only for the patient but also for universities and companies^[20]. According to the National Institute for Educational Studies and Research (INEP), only 1,357 students with ASD were identified in universities in 2018^[21]. However, once hired by companies, these individuals demonstrated improved performance in social interactions, teamwork, communication, problem-solving, and family relationships^[22].

Diagnosis

According to the DSM-5, to classi-

fy and diagnose ASD, the patient must meet four criteria: A, B, C, D, and E.

Criterion A consists of persistent deficits in social communication and social interaction. Therefore, nonverbal behaviors, limited socialization, and difficulty maintaining relationships are among the characteristics of this criterion. Criterion B refers to restricted and repetitive patterns of behavior, interests, or activities. In other words, repetitive movements, narrow hyperfocus, inflexibility regarding routines, and heightened or diminished sensory sensitivity may be part of the presentation. Criteria C, D, and E, on the other hand, are more concise. All three encompass the presence of symptoms since childhood (C), significant functional impairment (D), and the exclusion of other conditions, such as communication deficits, ADHD, etc. (E).^[1]

However, according to the ICD-11, the following symptoms must be present for a diagnosis:

- Difficulty initiating or maintaining social interactions;
- Inappropriate verbal or nonverbal responses in conversations;
- During communication, spoken language is combined with nonverbal gestures;
- Poor social awareness, leading to inappropriate behaviors;
- Ability to imagine and understand other people's feelings;
- Mutual interest in sharing one's own interests;
- Ability to maintain relationships with people who share the same atypical traits;
- Inflexibility and repetitive behaviors, interests, or activities that are clearly atypical and excessive;
- Poor adaptation to new situations and experiences associated with stress;
- Adherence to and inflexibility regarding routines;
- Excessive adherence to rules;
- Persistent and excessive behavior

ral rituals;

- Motor stereotypies;
- Excessive preoccupation with one or more special interests;
- Hyper- or hyposensitivity to sensory stimuli;
- Symptoms typically appear during childhood, although some may appear during adulthood;
- The symptoms significantly impact personal, family, social, educational, occupational, and other relationships^[23]

Masking

ASD symptoms may be present early in development; however, children who are not properly diagnosed end up engaging in “masking”—particularly women—where socialization is so demanding that individuals use this strategy to conceal or mask behaviors characteristic of ASD in order to adapt to the society in which they live^[24].

Treatment

There is no cure for ASD. However, there are ways to alleviate symptoms through multidisciplinary teams, such as therapists, speech-language pathologists, and medication. The earlier treatment begins, the better the results^[25].

CANNABIS

The Cannabis Family

Cannabis sativa is a plant in the Cannabaceae family^[26]. Currently, more than 500 chemical constituents have been identified in Cannabis sativa. However, only 100 of these are considered phytocannabinoids^[27]. Two of the most researched and studied are tetrahydrocannabinol (THC) and cannabidiol (CBD)^[28].

In short, THC is psychoactive, altering an individual's mental state and producing the commonly known sensation of “euphoria.” CBD, on the other hand, has no psychoactive effects and acts on the central nervous system,

but does not produce psychedelic effects. CBD is generally the treatment of choice in medical applications because it is typically well-tolerated and carries no risk of addiction^[29].

CBD Metabolism

The endocannabinoid system (ECS) is a biological system responsible for regulating various physiological functions, such as mood, appetite, pain, and immune response. It consists of endocannabinoid receptors, cannabinoids, and enzymes that catalyze their breakdown^[30].

Cannabinoid receptors are distributed throughout the body and interact with both the endocannabinoid system and exogenous cannabinoids. The main receptors are CB1 and CB2; the former is associated with the regulation of cognitive and motor functions and pain control, while the latter promotes the regulation of inflammation and immune responses^[26].

CB1 receptors are among the most abundant identified in the central nervous system (CNS), regulating cognitive function and emotions in neural circuits of the cortex, hippocampus, and amygdala. They can produce effects such as (1) decreased sensitivity to painful stimuli, control of movement, and inhibition of short-term memory (2) action on the hypothalamic-pituitary-adrenal axis and promotion of anxiolytic effects (3) modulation of the immune and inflammatory response (7) antitumor activity (8) modulation of food intake due to the release of hypothalamic hormones and steroids^[29].

Drug Interactions

When CBD is metabolized in the liver by cytochrome P450 enzymes, it inhibits the CYP2D6 enzyme, which is essential for the metabolism of various medications. Consequently, it may end up enhancing and promoting the effects of medications such as selective serotonin reuptake inhibitors (SSRIs),

tricyclic antidepressants, antipsychotics, beta-blockers, and opioids. Therefore, it is important to monitor patients who are undergoing treatment with CBD and taking any of these medications^[28].

Antiepileptic Drugs

CBD may interact with various antiepileptic drugs—seizures are common in individuals with ASD—by inhibiting the CYP2C19 and CYP3A4 enzymes, leading to an accumulation of N-desmethyl clobazam (nCLB) and activating the metabolism of cloba-

zam. Consequently, the affected individual may experience a potentiation of the effect of the clobazam-based medication, since nCLB is approximately 20–100% more potent than the substance itself^[28].

Nervous System

It is important to be alert to CBD side effects in individuals predisposed to psychiatric disorders, such as psychosis; it is crucial to administer the correct dose so that the patient's brain development is not affected and cognitive decline does not occur. It is also

important to exercise caution when combining THC use in patients, as this substance is a CB1 receptor agonist, producing psychoactive effects.

CONCLUSION

In summary, the findings suggest that the use of CBD may be a promising approach for managing ASD symptoms, with a relatively favorable safety profile. However, long-term studies are needed to validate its efficacy and safety.

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