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Review article

The use of cannabis in autism spectrum disorder: a systematic review and meta-analysis

O uso do cannabis no transtorno do espectro autista: revisão sistemática e metanálise

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Resumo

Objetivo: investigar as evidências do tratamento do transtorno do espectro autista com cannabis, buscando-se registrar os benefícios dessa proposta terapêutica em pacientes. **Métodos:** estudo de revisão sistemática, conduzido conforme as diretrizes PRISMA. Foram consultadas as bases de dados PubMed, BVS (LILACS e MEDLINE), Biblioteca Cochrane, Web of Science e Scopus. A qualidade e a validade interna dos estudos foram avaliadas por meio do *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE), da escala LONEY e da escala PEDro. Para a confecção da metanálise, foi utilizado modelo de efeito aleatório e teste de heterogeneidade. A respeito da análise de heterogeneidade, foram utilizados os testes Q de Cochran e o I^2. Foram considerados aceitáveis valores de I^2 abaixo de 25%. Para o cálculo do peso ou contribuição de cada estudo, foram utilizados modelos de efeitos aleatórios. O intervalo de confiança utilizado foi de 95% e valor p significativo <0,05. Foram avaliadas na metanálise, as escalas ADOS-2, VABS e CARS. **Resultados**: foram identificados 12 estudos, sendo cinco observacionais e sete clínicos randomizados. Estudos de vários países e com amostras heterogêneas indicam que há associação positiva entre o uso de cannabis e desfechos positivos no tratamento do transtorno do espectro autista. A metanálise, revelou-se que o uso de cannabis não modificou os resultados identificados na escala avaliativa ADOS-2, entretanto, os dados dos testes CARS e VABS mostraram significância estatística a favor do grupo experimento. **Conclusão:** a cannabis e os canabinóides podem ter efeitos promissores no tratamento dos sintomas relacionados ao TEA, podendo ser utilizados como alternativa terapêutica no alívio desses sintomas.
Palavras-chave: Transtorno do Espectro Autista. Canabinoides. Canabidiol.

Abstract

Objective: to investigate the evidence for the treatment of Autism Spectrum Disorder with cannabis, aiming to document the benefits of this therapeutic approach in these patients. **Methods:** a systematic review study conducted following PRISMA guidelines. PubMed, BVS (LILACS and MEDLINE), Cochrane Library, Web of Science, and Scopus databases were consulted. The quality and internal validity of the studies were assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), LONEY scale, and PEDro scale. Random-effects models and heterogeneity tests were used for meta-analysis, with Cochran's Q and I^2 tests for assessing heterogeneity. I^2 values below 25% were considered acceptable. Random-effects models were used to calculate the weight or contribution of each study. A 95% confidence interval and a significance level of $p < 0.05$ were considered. ADOS-2, VABS, and CARS scales were evaluated in the meta-analysis. **Results:** twelve studies were identified, including five observational and seven randomized clinical trials. Studies from various countries with heterogeneous samples suggest a positive association between cannabis use and positive outcomes in the treatment of Autism Spectrum Disorder. The meta-analysis revealed that cannabis use did not alter the results identified in the ADOS-2 assessment scale; however, data from CARS and VABS tests showed statistical significance in favor of the experimental group. **Conclusion:** cannabis and cannabinoids may have promising effects in treating symptoms related to ASD, serving as a therapeutic alternative in alleviating these symptoms.
Keywords: Autism Spectrum Disorder. Cannabinoids. Cannabidiol.

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in communication and social interaction and restricted/repetitive behavioral presentations, with the first symptoms appearing around the age of three. The literature shows that there is great variation in the type and severity of ASD symptoms[1,2].

Studies show that the prevalence of autism has increased by 178% since 2000[3]. It is estimated that ASD affects 1% of the population, and boys are four times more likely to be diagnosed with autism than girls[4].

Individuals with ASD have atypical cognitive functions, including executive and emotional dysfunction, atypical perception, impaired social cognition and perception, and information processing, which is usually correlated with attention deficit, as well as reduced verbal and non-verbal communication during interactions, including less eye contact and body language[3,6].

The main cause of the disease is unknown[2]. Although environmental factors play a role in the disease, there is evidence that genetic factors also act synergistically in ASD. Studies in this area have been carried out to evaluate the effects of factors such as maternal obesity, bleeding during pregnancy, low birth weight (less than 2,500 grams), drug use during pregnancy, intrauterine growth retardation (IUGR), not breastfeeding, small for gestational age (SGA)[2], maternal age, preterm labor[2,5] and low vitamin D levels5 during pregnancy, concluding that all are associated as risk factors for the disorder.

Although ASD patients experience a variety of disabling symptoms - including irritability, hyperactivity, inappropriate speech, social withdrawal, and mood symptoms such as anxiety - no established pharmacological treatment is available for the main symptoms of ASD. The US Food and Drug Administration has approved only two agents, aripiprazole and risperidone, for the treatment of irritability in ASD. The use of most of the other drugs is off-label, with uncertain therapeutic efficacy. In this context, identifying other pharmacological agents that are effective against the core and associated symptoms of ASD remains an important clinical issue for improving the quality of life of patients and their families who are directly impacted[4,6].

As discussed, although ASD in some cases requires pharmacological treatment, behavioral therapy remains the basis of treatment for symptoms of communication deficits, social interaction deficits, and repetitive behavior[6].

Against this backdrop, this study aimed to carry out a systematic review and meta-analysis on the effect of treating autism spectrum disorder with cannabis, to record the benefits of this therapeutic proposal in these patients.

Methods

This was a descriptive systematic review, conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendation[7]. The research question was delimited by applying the PICO[8] strategy, as follows: population (P): patients with a formal diagnosis of ASD; intervention (I): use of cannabis to treat ASD; control (C): patients not treated with cannabis (O): control of symptoms resulting from ASD. The study's guiding question was constructed by consulting the specialized literature on the subject: What is the evidence for treating autism spectrum disorder with cannabis?

Data collection was conducted by consulting the PubMed databases of the National Library of Medicine, responsible for coordinating the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Virtual Health Library (VHL), coordinated by the Latin American and Caribbean Center on Health Sciences Information (BIREME), with the VHL search tools defining the Latin American and Caribbean Health Sciences Literature (LILACS) and MEDLINE databases, the Cochrane Library, Web of Science and Scopus. The selected articles were published in the last five years (2018 to 2023) and no language restrictions were applied.

The descriptors used to search for studies are registered on the Medical Subject Headings (MeSH) platform and are treatment/tratamiento AND cannabis/cannabis AND autism spectrum disorder/trastorno del espectro autista, adapted for different databases, when necessary, using the Health Sciences Descriptors (DeCS), defined as autism spectrum disorder, cannabinoids, and cannabidiol.

This review included randomized clinical trials and observational studies. The inclusion criteria required that each study contained a formal diagnosis of ASD by DSM-5 or ICD-10, and no identified cause was required. There was no age limit for the patients in the studies. The presence of direct intervention with the use of cannabis in patients was evaluated and studies that evaluated the benefits or harms of the use of the substance were included.

The following were excluded: term papers, monographs, dissertations and theses, integrative and systematic review articles, research with a qualitative approach, books or book chapters, editorials, opinion articles, and abstracts.

For data collection, an instrument validated by Ursi (2005) was drawn up, including the following categories of analysis: identification code, title of publication, author and author's education, source, year of publication, type of study, region in which the research was carried out and the database in which the article was published. After selecting the articles, the information to be extracted from the studies was defined.

To enable the information to be captured, a database was created using Microsoft Office Excel 2010 software, consisting of the following variables: article title, year of publication, study design, and main outcomes. The data obtained was grouped into a table and thematic approaches and interpreted according to the specific literature. Data collection took place between May and November 2023 and was prepared according to the flowchart below (Figure 1), following PRISMA recommendations[7].

The internal validity and quality of the productions were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[9], the LONEY scale[10] and the PEDro scale[11-13].

The GRADE system consists of a manual to help researchers construct scientific investigations with what is known as Evidence-Based Health. GRADE is applied as a mechanism for assessing the quality of the findings and the strength of the study's recommendations, based on criteria that make it possible to downgrade or upgrade the level of evidence. It should be noted that the level of evidence shows confidence in the data contained in studies and is classified into four levels: (1) high; (2) moderate; (3) low; and (4) very low[9].

The LONEY scale is used to assess the methodological quality of cross-sectional studies. It consists of eight items, to each of which a point is assigned, and when considered appropriate, it displays scores ranging from 0 to 8 points[10].

On the other hand, the PEDro scale is used in randomized or quasi-randomized controlled studies to analyze their internal validity or statistical validity - a situation in which the scientific production presents sufficient statistical data for its results to be interpreted and analyzed. Its score varies between 0 and 10 points[11-13]. The higher the score achieved in both instruments, the better the representativeness of the validity and quality of the studies evaluated[10-12].

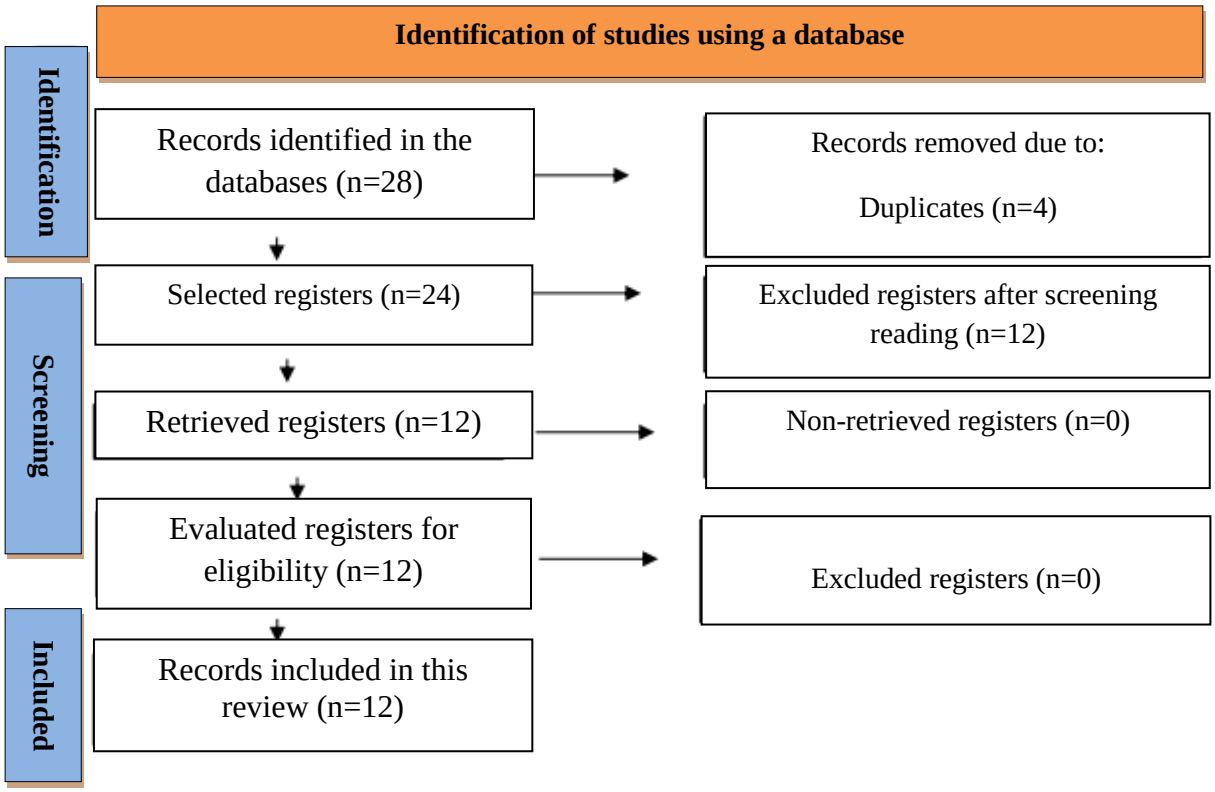
The meta-analysis used a random-effects model and a heterogeneity test. Concerning the heterogeneity analysis, Cochran's Q test and the I^2 test were used. I^2 values below 25% were considered acceptable.

Random effects models were used to calculate the weight or contribution of each study. In this case, weights were assigned based on both the variability within studies and the variability between studies.

The Funnel Plot graph was not used to investigate the presence of publication bias or selective bias in the studies included in the meta-analysis because only two studies were selected.

The confidence interval used was 95% and the p-value was significant <0.05. The ADOS-2, VABS, and CARS scales were evaluated in the meta-analysis.

Figure 1. Flowchart of the study selection process, 2023.



Results

This investigation consisted of twelve (12) scientific studies. Chart 1 shows the distribution of the selected studies, stratified by: authors, year of publication, instruments, study design, sample, main outcomes, and classification of methodological quality assessed by the GRADE system, the PEDro scale, and the LONEY scale.

Using the eligibility criteria, a total of 28 articles were identified. Of these, 4 were excluded because they were duplicates in the databases and 12 because they were systematic review studies, so 12 articles were selected for the final sample. The countries of origin of the studies included in this systematic review were Australia, Brazil, the United States, England, and Israel. The studies selected were published exclusively in international journals between 2018 and 2023.

The studies included in the review followed a total of 3,074 people with ASD, and the most applied tools for diagnosing patients in the studies were the DSM IV and V, ICD 10, and only one production considered ASD diagnosed by a qualified doctor or behavioral health clinician. In terms of how the medication was used, oral administration prevailed (83%). Other formulations used were vaporization, inhalation, oil, and spray, and there was unanimous agreement that the maximum safe dose was 600mg of cannabidiol (CBD) a day. The impact on various cognitive domains among the studies was evaluated, with the most important being quality of life, sleep quality, behavior,

communication, and anxiety. To assess the association with the recorded outcomes, the studies predominantly used the paired t-test (41.7%), followed by an analysis of variance (ANOVA) (33.3%) and multivariate analysis using logistic regression (25%).

Concerning methodological quality assessed using the GRADE system, most of the studies were classified as having a high level of evidence (58.3%). About measuring the quality of observational studies using the LONEY scale, the average score of the selected studies was 5.17 (95%CI: 3.49-6.85; SD: 1.60). The clinical trials selected had a mean score of 9 (95%CI: 8.06-9.94; SD: 0.89) on the PEDro scale.

After evaluating the articles obtained in the systematic review, only two randomized studies presented data that shared the same patient assessment scales, which is why only these two studies were chosen for the meta-analysis. The use of cannabis did not modify the results identified in the ADOS-2 evaluation scale. However, the data from the CARS and VABS tests showed statistical significance in favor of the experimental group. Fig. 2-4

Chart 1. Methodological evaluation of the studies that assessed the evidence for the treatment of ASD with cannabis (n=12).

Articles							Ratings		
Authors/year	**Place of study**	**Instruments**	**Design**	**Sample (n)**	**Statistical test**	**Main outcomes**	**GRADE**	**PEDro**	**LONEY**
Pretzsch, Voinescu et al. / 2019	London	*Autism Diagnostic Observation Schedule* (ADOS) and Autism Diagnostic Interview-Revised (ADI-R).	Randomized clinical trial	34 participants.	One-way ANOVA and t-test.	- Especially in ASD, CBD alters the fractional amplitude of regional low-frequency fluctuations (fALFF) ($p = 0.048$) and functional connectivity ($p = 0.026$; $p = 0.045$; $p = 0.017$; $p = 0.02$; $p = 0.027$; $p = 0.043$) in/between regions consistently implicated in ASD. - These factors may play important roles in language, movement, social, and visual word processing in ASD patients.	1	10	-
Pretzsch, Freyberget al. / 2019	United Kingdom	*Autism Diagnostic Observation Schedule* (ADOS) and Autism Diagnostic Interview-Revised (ADI-R).	Randomized case-control study	34 participants.	ANOVAs and Bonferroni test.	- CBD can "shift" the levels of Glx ($p = 0.033$) and GABA+ ($p = 0.004$). These metabolites contribute to the regulation of excitatory and inhibitory neurotransmission in both typical and autistic brains. However, the study also demonstrated that the atypical (autistic) brain reacts differently to the GABA+ CBD challenge. - The findings that the GABAergic system is distinct in ASD, but can be altered, are relevant to both understanding causal mechanisms and finding treatment targets in ASD.	1	10	-
Adams et al. / 2019	United States of America	Structured questionnaires.	Observational study	156 participants.	-	- The main benefits reported were calming effects, including improvements in anxiety, irritability, aggression/ agitation, hyperactivity, and sleep. There were also improvements in ASD symptoms. There were few adverse effects for THC/CBD and CBD and mild ones for marijuana.	3	-	4

Teixeira et al. / 2019	Brazil	Questionnaires constructed by the authors, using a Likert scale.	Observational study	15 children and adolescents aged between 6 and 17 years.	-	- The reported results are very promising and indicate that CBD-enriched CBD can improve multiple ASD symptoms, even in non-epileptic patients, with a substantial increase in quality of life for both ASD patients and caregivers.	3	-	4
Barchel et al. / 2019	Israel	Structured questionnaire and clinical assessment.	Randomized clinical trial	53 children and young adults aged 3 to 25.	Frequency and percentage analysis, standard deviation, mean, median, and range or interquartile range, and binominal test	- A comparison of symptom improvement between CBD treatment and conventional treatment was analyzed using the binomial test. Parents' reports suggest that CBD can improve ASD-related symptoms.	3	-	4
Aranet al./ 2021	Israel	Childhood Autism Rating Scale - Second Edition (CARS2-ST), Household Situations Questionnaire - Autism Spectrum Disorder (HSQ-ASD), Social Responsiveness Scale-II (SRS-2, Hebrew version).	Randomized clinical trial	186 children and young people aged between 5.5 and 21.	T-test, Pearson's chi-square test, multivariate, and linear logistic regression analysis.	- There was evidence that the use of cannabis, administered for 3 months, is well tolerated. - On the other hand, the evidence for the effectiveness of these interventions is mixed and insufficient.	1	9	-
Schnapp et al. / 2022	Israel	*Children's Sleep-Habit Questionnaire* (CSHQ) and the Social Responsiveness Scale.	Randomized clinical trial	150 children and adolescents aged 5 to 21.	Two-tailed paired t-tests or ANOVA, chi-square test, and protocol analysis.	- Regardless of the treatment (cannabinoids or placebo), improvement in sleep habits was associated with improvement in core autistic symptoms, as indicated by the total scores on the Social Responsiveness Scale (period 1: r = 0.266, p = 0.008; period 2: r = 0.309, p = 0.004).	1	8	-

Hacohen et al. / 2022	Israel	Social Responsiveness Scale, Autism Diagnostic Observation Schedule, teste Wechsler e teste de Vineland.	Randomized clinical trial	82 children and young people aged between 5 and 25.	Multiple regression analysis.	- Significant improvements were recorded in the severity of autism symptoms ($p = 0.003$); in the components of social affect and restricted/repetitive behavior ($p = 0.001$); and in the main symptoms of ASD among those who completed the treatment ($p = 0.043$). - There was also an improvement in communication ($p = 0.008$); daily life ($p = 0.007$); and socialization ($p < 0.001$). - The analyses revealed no significant impact of the treatment on any of the cognitive subtests ($p > 0.05$).	1	9	-
Erridge et al. / 2022	United Kingdom	Generalized Anxiety Disorder Scale (GAD-7), EQ-5D (EQ-5D-5L) and Sleep Quality Scale (SQS).	Case series study	74 participants.	Shapiro-Wilk test, paired t-test, Wilcoxon signed rank test, and Benjamini-Hochberg procedure.	- There were significant improvements in general health-related quality of life and sleep ($p < 0.010$). - There were significant reductions in the severity of anxiety ($p < 0.001$).	3	-	5
Silva-Júnior et al. / 2022	Brazil	*ASD symptoms and the Autism Treatment Evaluation Checklist*.	Randomized clinical trial	60 children aged 5 to 11.	Two-way mixed analysis of variance (ANOVA).	- Significant improvements were found in social interaction ($p = 0.002$); anxiety ($p = 0.016$); psychomotor agitation ($p = 0.003$); and the number of daily meals ($p = 0.04$). - There were improvements in concentration in children with mild autism ($p = 0.01$).	1	8	-

Cairns et al. / 2023	Australia	Structured questionnaires.	Case series study	297,904 participants with psychiatric indications (2,206 individuals with ASD).	Non-linear regression and correspondence analysis.	- A higher proportion of this therapy was recorded in men (65.1%) than in women (34.5%). - The 25-39 age group (46.2%) was predominant in terms of indications for the therapy. - There was a clear association between age group and indication ($p < 0.001$). - There is a lack of evidence-based clinical guidelines on the use of medical cannabis in psychiatry and the benefits for prescribers.	1	-	8
Rose et al. / 2023	United States of America	Adaptive Behavior Assessment System (ABAS-3); Behavior Assessment System for Children (BASC-3); and Social Responsiveness Scale (SRS-2).	Observational study	24 children and adolescents aged between 6 and 12.	T-test and Count Patient Diff Up Downs algorithm.	- Improvements were reported in emotional regulation (86.7%); behavioral regulation (86.7%); negative/aggressive behaviors (76.9%); attention (92.6%) and restricted/repetitive behaviors (73.3%). - Data demonstrate the potential of pharmacometabolomic to identify metabolic biomarkers that respond to CM treatment ($p < 0.05$), which can be used to build metabolic profiles for future personalization of CM treatment in children with ASD.	2	-	6

CBD: Non-intoxicating component cannabidiol.
CM: Medical cannabis.
EC: Cannabis sativa.
ASD: Autistic Spectrum Disorder.

Figure 2. Forest Plot 1.Meta-analysis with random effect model on the effect of cannabis use on the ADOS-2 test. Despite presenting an acceptable heterogeneity of I^2=25, it revealed that the experiment group did not present statistical significance in the results.

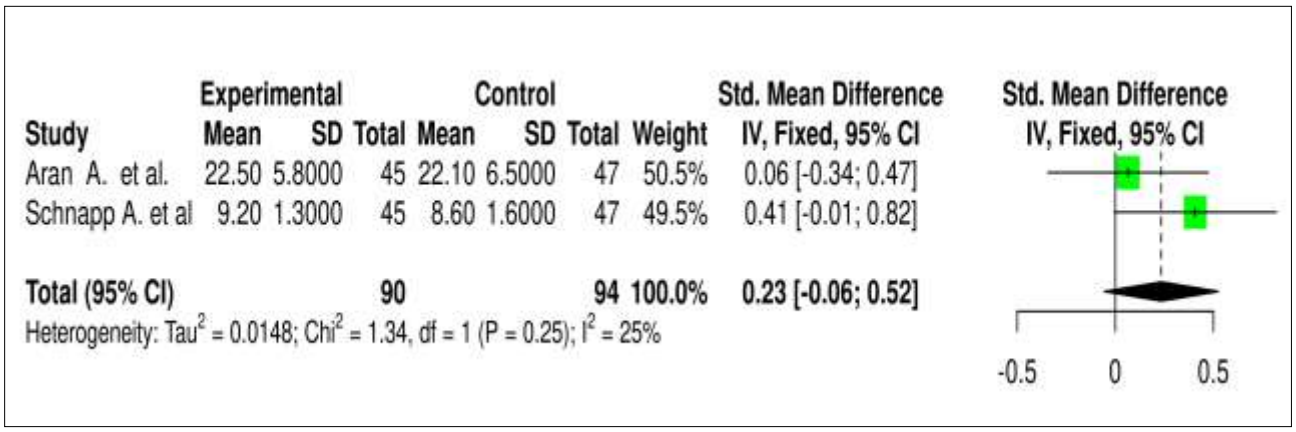


Figure 3. The meta-analysis with a random effect model on the effect of cannabis use on the CARS test showed low heterogeneity I^2=0 with statistical significance in the results in favor of the experiment group. On this scale, the higher the score obtained, the greater the likelihood of a diagnosis of autism spectrum disorder (ASD).

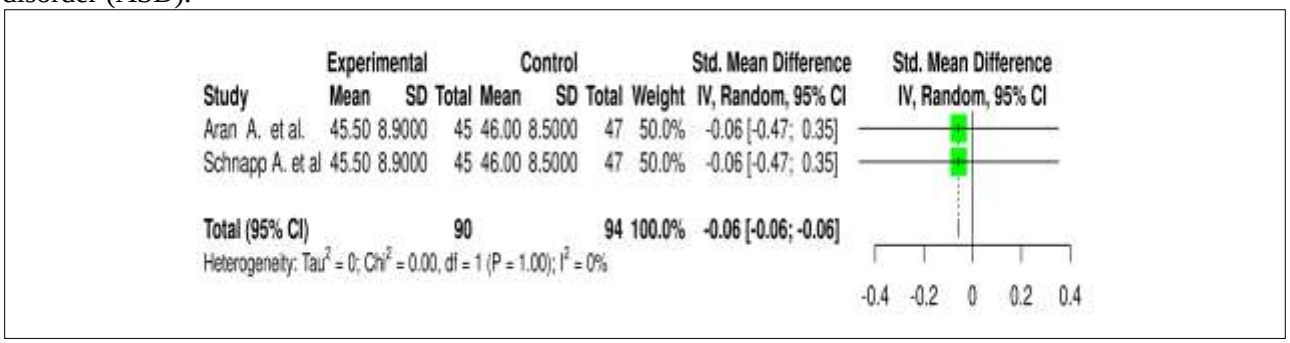
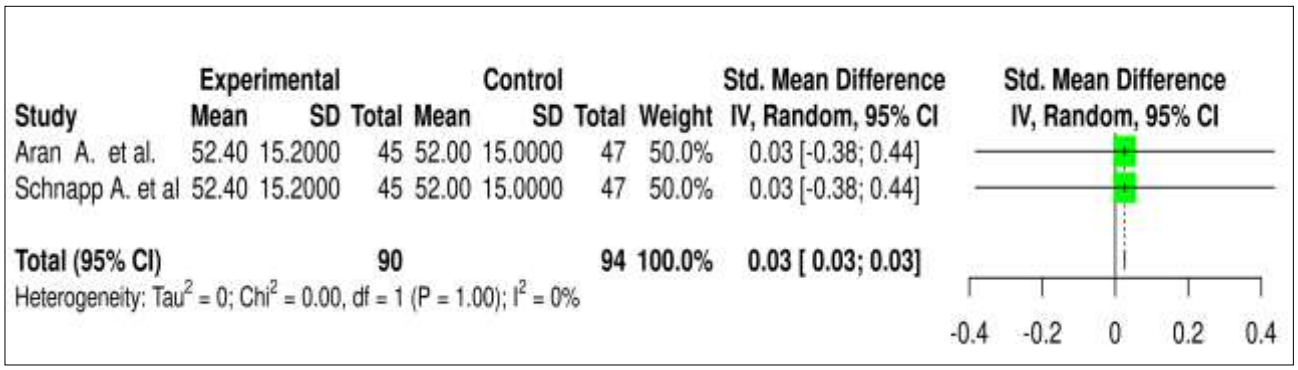


Figure 4. The meta-analysis with a random effect model on the effect of cannabis use on the VABS test showed low heterogeneity I^2=0 with statistical significance in the results in favor of the experiment group. On this adaptive behavior scale, a higher score indicates a better degree of adaptation in the areas of communication, social skills, daily living and motor skills. Higher scores indicate a higher level of adaptive skills compared to people in the same age group.



Discussion

This review provides information on the use of cannabinoids as a therapeutic proposal for autism spectrum disorder, highlighting the main outcomes and benefits recorded in the studies included here.

Of note is a case series study carried out in Australia, which found a higher proportion of cannabidiol (CBD) therapy in men (65.1%) compared to women (34.5%). In addition, the authors observed that the 25 to 39 age group (46.2%) was predominant with psychiatric indications for therapy - including ASD. There was also a clear association between age group and treatment indication ($p < 0.001$)[14].

A randomized clinical trial carried out in Israel - following 82 children and young people aged between 5 and 25 undergoing treatment with medicinal whole plant cannabis extract infused in medium-chain triglyceride (MCT) oil with a CBD: THC ratio of 20:1, recorded significant improvements in the severity of autism symptoms ($p = 0.003$); in the components of social affection and restricted/repetitive behavior ($p = 0.001$); and in the main symptoms of ASD among those who completed the treatment ($p = 0.043$)[15].

Furthermore, the authors observed improvements in communication ($p = 0.008$); daily life ($p = 0.007$); and socialization ($p < 0.001$).On the other hand, the analyses did not reveal any significant impact of the propaedeutic on any of the cognitive subtests ($p > 0.05$)[15]. Treatment with cannabis seems to have a positive effect - reported by the parents/family members of autistic patients - more consistently on social symptoms and particularly in cases with initially more severe psychosocial pathognomonic features[15-17].

Similarly, another observational survey conducted with children and adolescents in the United States (USA) found reports of improvements in psychosocial domains, such as emotional regulation (in 86.7% of the group); behavioral regulation (86.7%); negative/aggressive behaviors (76.9%); attention (92.6%); and restricted/repetitive behaviors (73.3%)[18].

Another randomized clinical trial carried out with children diagnosed with ASD found significant improvements in social interaction ($p = 0.002$), anxiety ($p = 0.016$), psychomotor agitation ($p = 0.003$), and the number of daily meals ($p = 0.04$) after therapy with cannabis extract over 12 weeks. There was also an improvement in concentration in children with mild autism ($p = 0.01$)[19]. Congruent results were reported in a study in the USA[20]. Regarding pharmacodynamic safety, only three children - representing 9.7% of the treatment group - showed adverse effects, specifically dizziness, insomnia, cramps, and weight gain[19].

Regarding the repercussions of cannabis on quality of life, another study carried out in the United Kingdom revealed that the substance provides significant improvements in general well-being related to health and sleep ($p < 0.010$)[22], which is consistently recorded in a study produced in Israel[23]. The authors also highlight the significant reductions in the severity of anxiety that the therapy generated ($p < 0.001$)[22].

From a biochemical and neurotransmission point of view, a study carried out in London found that CBD can improve levels of glutamate + glutamine (Glx) ($p = 0.033$) and GABA+ ($p = 0.004$). These molecules contribute to the regulation of excitatory and inhibitory neurotransmission in both typical and autistic brains. They play an important role in learning, respectively, and have a relaxing function and act to reduce anxiety, stress, and fear[24].

Two studies that took part in this meta-analysis evaluated therapeutic responses based on the CARS (Clinical Assessment of the Relationship Between Self and Others) test, in which the score obtained can vary from 15 to 60 points. In this test, the higher the score obtained by the patient, the greater the likelihood of an ASD diagnosis. Statistical significance was observed in the results in favor of the experimental group[21,23].

This meta-analysis also evaluated the results of two studies that applied the VABS (Vineland Adaptive Behavior Scales). This test assesses performance, and higher scores are associated with a higher level of adaptive skills when compared to people of the same age group. The meta-analysis found statistical significance in favor of the experimental group[21,23].

On the other hand, it is important to note that in an investigation carried out in Asia with 186 children and young people - aged 5.5 to 21 - diagnosed with ASD, it was found that the use of Phyto cannabinoids - administered for 3 months - is well tolerated, although evidence of the effectiveness of this therapy was insufficient or, at the very least, mixed[21]. Congruently, another study conducted in Oceania also found no significant prospects of benefit or efficacy of the substance[14]. The researchers state that there is a lack of evidence-based clinical guidelines on the use of medical cannabis in psychiatry and the benefits for prescribers, thus making it necessary to conduct a relevant line of studies on the efficacy of the therapy in neurobehavioral disorders[14,21].

Additionally, it should be noted that, especially in ASD, CBD alters the fractional amplitude of regional low-frequency fluctuations (fALFF) ($p = 0.048$) and functional connectivity ($p = 0.026$; $p = 0.045$; $p = 0.017$; $p = 0.02$; $p = 0.027$; $p = 0.043$) in/between neural regions consistently implicated in ASD. These factors may play important roles in language, movement, social, and visual word processing in patients with ASD[25].

Among the limitations of this study, it can be noted that this meta-analysis involved only two studies, with a relatively small number of participants. Another point to consider is the differences between the concentrations and dosages used to treat the control group, as well as the epidemiological characteristics of the participants, which could provide different therapeutic responses.

Conclusion

Cannabis and cannabinoids may have promising effects in the treatment of ASD-related symptoms, with an impact on the quality of life of autistic individuals. By reducing the symptoms of this neurobehavioral disorder, they can be used safely as a therapeutic alternative. However, randomized, blind, placebo-controlled clinical trials, especially multicenter ones, are still needed to clarify the results of the effects of cannabis and its cannabinoids on people with ASD, as well as the possible side effects of their use. Another meta-analysis involving a larger number of studies would be of great scientific value.

Conflict of interest

The authors declare no competing interests.

Authors' contributions

The authors have approved the final version of this article and declare themselves responsible for all aspects of the manuscript, such as integrity, originality and accuracy.

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