Chapter 43

Effects of the use of cannabidiol in the treatment of psychiatric diseases: a quick literature review

10.56238/tfisdwv1-043

Vicente Gabriel Winck Mattos
Federal University of Rio Grande, Rio Grande, Brazil
E-mail: vgwmattos@gmail.com

Gabriel Henrique Ellwanger Freire
Federal University of Rio Grande, Rio Grande, Brazil

Anna Letícia Coutinho Dos Santos Valladares
Federal University of Rio Grande, Rio Grande, Brazil

Luana Raquel Karkow Wojciechowski
Federal University of Rio Grande, Rio Grande, Brazil

ABSTRACT
Objective: To carry out a quick review of the literature on the use of cannabidiol (CBD) in the treatment of psychiatric illnesses, in order to identify the benefits and adverse effects of using this substance for this purpose. Methods: A search was carried out in the PubMed database with the descriptors: "mental disorders" OR "mental illness" OR "psychiatric disease" OR "psychiatric disorder" AND "treatment" AND "cannabidiol". Randomized clinical trials evaluating the efficiency of CBD in the treatment of psychiatric illnesses were included. The selection of titles, abstracts and articles read in full was performed in pairs and the Rayyan platform was used to manage the references. Result: 304 articles were identified in the PubMed database, after reading the titles, 87 abstracts were read and, of these, 21 articles were selected for full reading. Finally, after applying the inclusion and exclusion criteria, 4 studies were selected for this review. The articles did not prove the effectiveness of cannabidiol in the treatment of the diseases addressed, as there was no association between the use of CBD and the improvement of symptoms, with one of the studies even pointing to an increase in anxiety levels with the use of CBD. The observed side effects were mild, such as nausea, tiredness, sedation and increased appetite. Conclusions: This rapid literature review was not able to demonstrate that cannabidiol is an effective treatment for psychiatric illnesses, as further studies are needed to prove such benefits.

Keywords: Cannabidiol, Treatment, Psychiatric Disorders, Psychiatric Illnesses.

1 INTRODUCTION

The Pan American Health Organization (PAHO)1, in 2019, classified psychiatric disorders as a combination of abnormal thoughts, perceptions, emotions and behaviors, generated by multiple chemical and psychological factors, which bring harm to individual, family and social life, since the symptomsof mental illnesses encompass a wide range of significant cognitive alterations. Moreover, it should be emphasized that psychiatric disorders are universal, since they affect individuals of all ages and ethnicities,causing serious and definitive incapacitations that increase the demand in health services2.

Among the factors that affect people's mental health, economic circumstances, lack of community support, stressful conditions, genetics, nutrition, perinal infections and exposure to environmental risks stand out1. The association of these situations provides for the worsening of psychiatric dysfunctions in more than 25% of the world population3.

Tadokoro4 states that the incidence of these pathologies in the global action populis worrisome, since four out of ten people present some manifestation of cognitive impairment, such as depression, bipolar affective disorder, schizophrenia, psychoses, dementia, intellectual disabilityand development disorders,

including autism. With regard to Brazil, the prevalence of mental disorders in the adult population varies between 20% and 56%, essentially affecting females and workers in the 21st century2.

As the research sector of the medical and scientific aspects advancesin the clinical and scientific aspects, relatively specific treatments for particular disorders or groups of symptoms are elaborated. That is, antipsychotic drugs are usually used to treat psychoses, that is,for disorders such as schizophrenia, in which psychosis is usually prominent, as well as for forms of mood disorders that favor the occurrence of psychotic symptoms5.

Flores and Zamin6 found that Cannabidiol (CBD) is an ethical non-psychotomime substance, presenting anti-inflammatory, neuroprotective, antipsychotic, analgesic, anticonvulsant, anti-emetic, antioxidant, antiarthritic and antineoplastic properties, and is therefore considered one of the most promising herbal medicines for the tr psychiatric disorders. This is because this substance can relieve several symptoms, such as anxiety, for example, since it has a calming effect on the Central Nervous System (CNS)7. It is then infers that CBD may play a relevant role inthe development of new therapeutic methods in various neuropsychiatric disorders.

In this sense, directing our research to Cannabidiol, the main phytocannabinoid present in Cannabis sativa, and we aim to conduct a rapid review of the literature to investigate the benefits and adverse events of this compound in the treatment of psychiatric disorders.

2 METHODS

On August 4, 2021, a search was conducted in the PubMed database, with the following descriptors: (((((mental disorders) OR (mental illness)) OR (psychiatric disease)) OR (psychiatric disorder)) AND (treatment)) AND (cannabidiol) with year-on-year filters (2016-2021). The review was produced in pairs, being a third member, coming from the opposite duo, responsiblefor defining the cases related to conflicts or doubts about the inclusion or exclusion of the article. Rayyan was used to organize the references. This review included studies in Portuguese, English and Spanish.

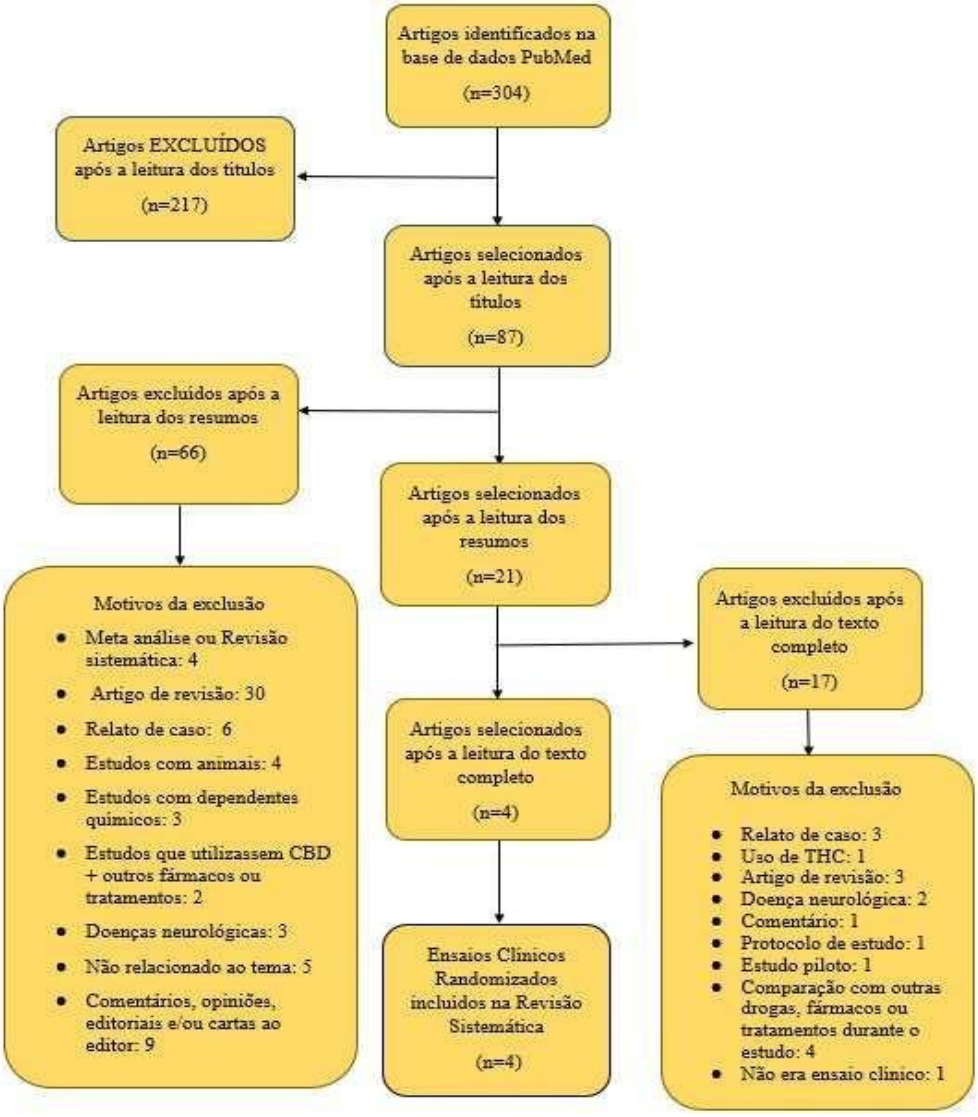
In this sense,articles containing randomized studies or clinical trials were included, testing Cannabidiol (CBD) in patients affected by some psychiatric disorder defined by dsm5. Therefore, we excluded: meta-analyses and systematic reviews, cross-sectional studies, case-control studies, case-control reports, studies developed with animals and individuals with neurological disorders and neurodegenerative diseases, as well as individuals with a history of chemical dependence. The selection process ispresented in the Flowchart (Figure 1).

The information extracted from the included articles were: author, year, country, study design, intervention period, disorder, number of participants, age group, number of individuals in the control group, main results and adverse effects. The information obtained from the selected articles is presented in Tables I, II and III.

3 FINDINGS

A total of 304 references were identified in the Pubmed database. After reading the titles, we eliminated 217 articles, thus leaving 87 studies. Then, in the process of reading the abstracts, 66 more references were excluded. Thus, we were left with 21 articles that were read in full and selected 4 papers for this review. This process is illustrated in Figure 1.

Figure 1: Diagram of the flow of the selection process of the articles in the different phases of the review.



Articles identified in the PubMed database =304
Articles EXCLUDED after reading the titles = 217
Articles selected after reading the titles = 87
Articles excluded after reading the abstracts = 66
Articles selected after reading the abstracts = 21
Articles selected after reading the full text =17
Articles excluded after reading the full text = 4

Reasons for exclusion:
Meta analysis or systematic review;
Review article;
Case report;
Animal studies;
Studies with drug addicts;
Studies using CBD plus other drugs or treatments;
Neurological diseases;
Not related to the topic;
Comments, opinions, editorials and/or letters to the editor.

Reasons for exclusion:
Case report
Use of THC;
Review articles;
Neurological disease;
Comment;
Study protocol;
Public study;
Comparison with other drugs, pharmaceuticals or treatment during the study;
It was not a clinical trial

The selected studies were double-blind randomized clinical trials. Among them, two had a parallel group of healthy individuals8,10. In addition, the articles chosen were published in English and developed in countries such as United Statesof America9 (1 articles)and United Kingdom 8,10,11 (3 articles). The characteristics and main results of the selected studies are presented in Tables I, II and III.

Table I: General characteristics of studies evaluating the use of cannabidiol (CBD) in the treatment of psychiatric disorders

STUDY	COUNTRY	OUTLINE	BELT AGE	DISORDER
APPIAH- KUSI et al., 2020	United Kingdom	Randomized double-blind study with parallel group.	Unspecified	Individuals with high clinical risk of developing psychosis.
BOGGS et al., 2018	USA	Randomized double-blind study.	18 - 65 years old	Individuals with chronic schizophrenia.
DAVIES et al., 2020	United Kingdom	Randomized double-blind study with parallel group.	18 - 35 years old	Individuals at high clinical risk of developing psychosis.
HUNDAL et al., 2017	United Kingdom	Randomized double-blind study.	18 - 50 years old	Individuals with anxiety and paranoia.

Table II: interventions used in randomized clinical trials with or without a parallel group.

STUDY	TIME ELAPSED	GROUP WITH CDB	PLACEBO GROUP	PARALLEL GROUP
APPIAH- KUSI et al., 2020	8 days	16 people ingested oral doses of 600 mg/day	16 people	26 healthy people
BOGGS et al., 2018	6 weeks	18 people ingested two oral doses of 300 mg (600 mg/day)	18 people	-
DAVIES et al., 2020	1 day	15 people ingested an oral dose of 600 mg	15 people	19 healthy people
HUNDAL et al., 2017	4h and 30 min	16 people ingested a dose 600 mg/day oral	16 people	-

Table III: main results found in selected articles

STUDY	MAIN RESULTS	ADVERSE EFFECTS
BOGGS et al., 2018	There was no significant association.	20% of participants in the CBD group reported mild sedation.
DAVIES et al., 2020	Group with CBD showed lower activation of the left parahippocampal gyre and left amygdala, also showed higher activation in the left and right putamen compared to the placebo group. Fear processing in the CBD group was intermediate in relation to the resultsof the control groups (placebo and healthy people).	Not specified.
HUNDAL et al., 2017	There was no significant association.	5 participants had tiredness/sedation. 2 participants had vertigo/dizziness. 2 participants had nauseas. 2 participants had increased appetite. 1 participants had abdominal discomfort (all mild conditions).

Among the selected studies, the treatment time ranged from 4.5 hours11 to 6 weeks9 (Chart II). The number of subjects in the case and control group (placebo) was balanced,with an average of 16.5 cases and 16.75 placebos, which allows an adequate analysis. In addition, two studies8,10 made a comparison between the group with psychiatric disorders and the group composed of healthy people, which is called parallel. In the study by Boggs etal. 9, participants used stable doses of antipsychotics for 3 months and, mainly, without alteration at 4 weeks prior to the evaluation.

In the four selected studies, the effects of the use of cannabidiol were not comparedto the results of other drugs, thus, they had only the objective of evaluating the effects of CBD in the treatment of patients with psychiatric disorders. The cannabidiol dosage administered to the participants of the 4 studies is related to the results previously obtained by other researchers, i.e., 600 mg/day, as there are indications that this dose would cause improvement in the symptoms of the disorders. In addition, this amount can be divided into two doses of 300 mg9 or into a single dose8,10,11.

Appiah-Kusi etal. 8 evaluated CBD modulation in neuroendocrine responses in patients at high clinical risk of developing psychosis (CHR). The participants underwent the screening of the Criterion of Personal Assessment and Evaluation of Crise (PACE), the parallel group was established by negative screening for mental disorders and the group of psychotics through psychosis screening questionnaire (PSQ). In addition, all were submitted to the STAI-S questionnaire, which assesses anxiety and negative feelings. Thus, in a unilateral variance analysis (ANOVA), they found a significant effect of the HC CHR-PLACEBO group, CHR-CBD ($p = 0.005$) on cortisol reactivity, as well as a significant linear decrease ($p = 0.003$) of this hormone. The alteration in cortisol related to the social stress test (TSST) was higher in the parallel group (HC) and lower in patients with CHR-PLACEBO, with participants in the group with CHR-CBD presenting an intermediate response. The contrasts showed that cortisol rand activity was significantly different in healthy patients compared to CHR-PLACEBO ($p = 0.003$) and in HC compared to CHR-CBD ($p = 0.014$). However, the cortisol reaction was not different between CHR-PLACEBO and CHR-CBD ($p = 0.70$).

Among the three groups of participants, there was a significant linear increase in the score ($p = 0.012$) in the STAI-S scores, which shows a change in anxiety and in the experience of public speaking stress, and the changes were higher in the groups withthe CHR in relation to the HC, with the CHR-PLACEBO presenting a higher response than the others, in HC the score was lower and the chr-CBD participants demonstrated an intermediate level when equated to the other groups.

Boggs etal. 9 evaluated the effects of cannabidiol on cognition and symptoms of patients with chronic schizophrenia, through the MATRICS Consensus Cognitive Battery (MCCB) and the Negative and Positive Syndromes Scale (PANSS). The participants werefound by the Hopkins Verbal Test (HVLT) screening and the IQ test, which was measured by the Wechler Adult Intelligence Scale.

In the knowledge tests, the researchers found that there was no main effect of the drug or time on themccb compound score. However, a significant effect of the × was observed ($p= 0.02$), revealing that

only subjects treated with placebo improved over time (p = 0.03). In addition, in the reasoning and problem-solving domain, measured by the MCCB, a trend towards a main effect of time (p = 0.07) and × drug interaction was observed for time (p = 0.04), but the analyses revealed that only participants treated with placebo improved over time (p = 0.009). Finally , PANSS scores decreased over time (p < 0.0001), but there was no significant interaction of drug x time (p = 0.18). Thus, CBD did not show significant results in improved performance in MCBB or psychotic symptoms.

Davies etal. 10 used magnetic resonance imaging to assess how individuals' brains, classified according to the Comprehensive Assessment of Mental States at Risk (CAARMS) as at high clinical risk of developing psychosis, would react to the imagens of faces with expressions of fear. In this study, three groups were used, one CBD and one placebo, composed of 15 individuals each, in addition to a parallel group, called "control", composed of 19 healthy individuals. It was found that the use of CBD resulta in images with "signature of anxiolytics", indicating that this substance is able to modulate the activity of anxiety-related regions of the brain, such as the amygdala. However, this change was not statistically considered significant. Inaddition, based on magnetic resonance imaging, the CBD group presented intermediate brain activity, having presented lower level of brain activity than the placebo group, but even higher than the control group.

In the Hundal study and speakers colab11 it was not possible to find significant associations between cbd use and improvement of the disorder, as well as there were indications of increased levels of anxiety with cannabidiol use. In this clinical trial, the aim was to analyze the effects of dand a single dose of 600mg of CBD on persecutory ideation and anxiety in individuals with high paranoid trait. Participants were submitted to stress situations with virtual reality (VR) and to measure the results were used the "State Social Paranoia Scale" (SSPS), the "Community Assessment of Psychic Experiences" (CAPE) that evaluates psychotic experiences, the "Beck's Anxiety Inventory" " (BAI) that addresses the three dimensions of affection: hedonic tone, energetic excitation and tense excitation. In addition, physiological parameters, such as heart rate, blood pressure and salivary cortisol levels, were followed up to evaluate the effects of CBD. The screening of the patients was performed using Green's ParanoidS Thought Scale. Thus, they were divided into 2 groups, CBD group, with 16 participants, and placebo group, also with 16 participants.

Regarding the parameters of affect evaluation and cognitive evaluation, it was found that there was no significant interaction between the RV session and the treatment with CBD. Regarding cortisol levels, measured 1 hour before ingestion of the CBD capsule, shortly after ingestion, 2h, 3h, 3.5h and 4.5h after, indicated an increasing reduction in levels of this hormone, with a small peak durante immersion in VR, but no difference was observed between the CBD group and placebo. Cardiovascular indices also did not indicate differences between the CBD group and placebo. However, the SSPS indicated that the CBD group had a higher score, although the distinção between the groups did not reach statistical levels of significance. In BAI, patients who received CBD had higher scores, which demonstrates interaction between session,

treatment and increased levels of anxiety. Still, according to cape, there was also no reduction in anxiety levels with the use of CBD.

In a general context, onlytwo studies 9,11 reported adverse effects of cannabidiol use, such as tiredness, sedation, vertigo, dizziness, nausea, abdominal discomfort and increased appetite. All reactions were considered mild intensity.

4 CONCLUSION

Based on the data obtained, it is not possible to state that CBD is an effective treatment for psychiatric diseases. Although the side effects reported in two of thestudies 9,11 are mild, which does not suggest contraindications to the use of this substance, the small number of randomized clinical trials found precludes an assertive decision. Moreover, the use of different methods in the analyzed studies to measurecbd ephemuses, together with the fact that the results are not convergent, regarding the existence of an association between the use of this phytocannabinoid and the improvement of psychiatric symptoms, therefore, make it impossible for CBD to be considered effective at this time.

In thisstudy, further studies are needed, with a randomized clinical trial design, in which the instruments and ways of measuring the results are standardized, establishing parameters that evaluate larger samples of individuals, as well as the use of other cannabidiol dosages, so that it is possible to verify the efficacy of this substance in the treatment of these diseases.

REFERENCES

1. Organização Pan-Americana de Saúde. Organização Mundial da Saúde (OMS). Mental disorders, novembro de 2019. Disponível em: <https://www.paho.org/pt/topicos/transtornos-mentais> Acesso em: 14 de agosto de 2021.

2. Santos, E. G.; Siqueira, M. M. Prevalence of mental disorders in the Brazilian adult population: a systematic review from 1997 to 2009. Jornal brasileiro de psiquiatria, 2010, 59 (3). https://doi.org/10.1590/S0047-20852010000300011.

3. Belangero, S. L. Opinião: Genética aplicada às doenças mentais e os principais resultados observados em suas pesquisas. Universidade Federal de São Paulo, 2020. Disponível em: <https://www.unifesp.br/reitoria/dci/releases/item/4708-opiniao-genetica-aplicada-as-doencas- mentais-e-os-principais-resultados-observados-em-suas-pesquisas>. Acesso em: 15 de agosto de 2021.

4. Takodoro, D. C. Transtorno mentais na atenção primária: uma reflexão sobre a necessidade de organizar e acolher a demanda dos usuários do SUS. Universidade Aberta do Sistema Único de Saúde, 2012. Disponível em: <https://ares.unasus.gov.br/acervo/html/ARES/4829/1/3398.pdf>. Acesso em: 16 de agosto de 2021.

5. Andreasen, N. C.; lopes, M. F.; black, D. W.; dornelles, C. Introdução à psiquiatria. 4. ed. Porto Alegre, RS: Artmed, 2009.

6. Flores, L. E.; zamin, L. L. Potencial neuroprotetor, antioxidante e anti-inflamatório do Canabidiol: relevância e perspectivas para o tratamento de doenças neurodegenerativas. Revista de Ciências Médicas e Biológicas, [S. l.], v. 16, n. 2, p. 224–229, 2017. DOI: 10.9771/cmbio.v16i2.20568. Disponível em: <https://periodicos.ufba.br/index.php/cmbio/article/view/20568>. Acesso em: 16 de agosto de 2021.

7. Jurkus, R.; Day, H. L. L.; Guimarães, F. S.; Lee, J. L. C.; Bertoglio, L. J.; Stevenson, C. W. “Cannabidiol Regulation of Learned Fear: Implications for Treating Anxiety-Related Disorders”, 2019 Aug 29;2019:2509129. doi: 10.1155/2019/2509129. eCollection 2019.

8. Appiah-Kusi E; Petros N; Wilson R; Colizzi; Bossong, M. G.; Valmaggia L; Mondelli V; McGuire P; Bhattacharyya S. Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis. Psychopharmacology (Berl). 2020 Apr;237(4):1121-1130. doi: 10.1007/s00213-019-05442-6. Epub 2020 Jan 8. PMID: 31915861; PMCID: PMC7113209.

9. Boggs D. L.; Surti T.; Gupta A.; Gupta S.; Niciu M.; Pittman B.; Schnakenberg A. M. M.; Thurnauer H.; Davies A.; D'Souza D.C.; Ranganathan M. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology (Berl). 2018 Jul;235(7):1923-1932. doi: 10.1007/s00213-018-4885-9. Epub 2018 Apr 5. PMID: 29619533.

10. Davies C.; Wilson R.; Appiah-Kusi E.; Blest-Hopley G.; Brammer M.; Perez J.; Murray R. M.; Allen P.; Bossong M. G.; McGuire P.; Bhattacharyya S. A single dose of cannabidiol modulates medial temporal and striatal function during fear processing in people at clinical high risk for psychosis. Transl Psychiatry. 2020 Sep 13;10(1):311. doi: 10.1038/s41398-020-0862-2. PMID: 32921794; PMCID: PMC7487274.

11. Hundal H.; Lister R.; Evans N.; Antley A.; Englund A.; Murray R. M.; Freeman D.; Morrison P. D. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. J Psychopharmacol. 2018 Mar;32(3):276-282. doi: 10.1177/0269881117737400. Epub 2017 Oct 31. PMID: 29086614.