LUMEN ET VIRTUS

The efficacy of cannabidiol in the treatment of mental disorders: A systematic review of double-blind randomized controlled trials

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ABSTRACT

INTRODUCTION: The therapeutic application of cannabidiol (CBD) is gaining interest due to the growing body of evidence supporting its use in the treatment of mental disorders. OBJECTIVES: To develop a systematic review to evaluate the scientific evidence supporting the use of CBD in the treatment of psychiatric disorders. METHODS: Only double-blind randomized clinical trials were used. The search for scientific evidence was carried out in the PubMed and VHL databases, with the descriptors "cannabidiol" and "mental disorders". Between 2020 and 2022, 219 articles were found in PubMed and 79 in the VHL. Review articles, observational studies, manuscripts, repeated articles, and articles that did not focus on the treatment of mental disorders by the use of cannabidiol were excluded. Thus, 10 relevant studies remained for the present systematic review. RESULTS: Of the 10 articles selected, 90% presented positive results for the use of CBD in the treatment of various mental disorders. Among them, there was a higher prevalence of drug use for the treatment of psychosis, anxiety and behavioral mechanisms; evidencing its usefulness and benefits. It was observed that in cases of psychosis, CBD significantly increased glutamate levels in the left hippocampus of patients, proving its effectiveness. In research involving behavioral mechanisms, it was possible to verify that the use of CBD linearly decreased the levels of cortisol linked to stress in the patient's body, evidencing its therapeutic capacity. CONCLUSION: The use of CBD was useful to relieve the symptoms of some mental disorders, such as psychosis, anxiety, schizophrenia, autism, behavioral problems and stress. In addition, research has still shown uncertain and sometimes even contradictory results, which reinforces the need for more research on the action of this drug in the treatment of mental disorders.

Keywords: Cannabidiol, Mental Disorders, Psychosis, Behavioral Mechanisms and Anxiety.

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INTRODUCTION

Cannabis sativa is a species of cannabis plant, in which it has been reported to be used medicinally within Chinese culture in the world's oldest pharmacology. However, at the end of the twentieth century, with the discovery of the endogenous cannabinoid system in the brain, interest in the pharmaceutical role of cannabis grew exponentially, due to the possible interaction of cannabis with the Central Nervous System (CNS) and its possible therapeutic effect. (KHAN et al., 2020).

Cannabis has more than 140 cannabinoid compounds, the one of main interest in the pharmaceutical industry, Cannabidiol (CBD), due to its therapeutic effect on various mental disorders (CITTI et al., 2018). Recent research (PINTO et al., 2020) observed the effectiveness of CBD in the treatment of epilepsy, which recorded an increase in the quality of life of these patients, with a significant improvement in the mood of these individuals.

In addition, it is possible to observe several studies that expose other benefits of the use of CBD in the management of psychological disorders. Cannabidiol has shown favorable results for the treatment of neuropsychological symptoms related to moderate and advanced stages of dementia, particularly agitation, aggressive behavior, sleep disturbance, and sexual disinhibition (STELLA et al., 2021). In addition, there are case reports of the use of CBD to reduce symptoms of depression and anxiety, including simple phobias and symptoms of paranoia and dissociation (LACZKOVICS et al., 2021).

Therefore, the growing number of studies that address the beneficial effects of this substance in relation to some mental disorders brings to light whether there is a real possibility of applying this drug in the treatment of these diseases. Thus, the objective of this systematic review is to evaluate the scientific evidence that supports the use of CBD in the treatment of mental disorders.

METHODOLOGY

The present systematic review was initially registered in the PROSPERO database under CRD number 405747 and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

This review was designed using the PICO (Population/Intervention/Control/Outcome) strategy; and the question that guided the research was: "Does the use of Cannabidiol (CBD) have a therapeutic effect in the treatment of psychological disorders?".

The searches were carried out in May 2022 in the electronic databases of the National Library of Medicine, USA, in its PubMed (www.pubmed.com.br) and VHL (https://bvsalud.org/) interface. The MeSH terms used were: "Mental Disorders" AND "Cannabidiol".

Randomized double-blind clinical studies, published from 2020 to 2022, in English, Portuguese, and Spanish, were included. The selection was made based on the title and abstract, and

then by reading and analyzing the full text. All citations were entered into the Mendeley Reference Manager.

From the included studies, data were extracted and tabulated regarding the disease that was the focus of the research, the use of placebo, the total sample of patients and the results obtained by the studies.

Based on a detailed evaluation of methodology and results, the following methodological inclusion criteria were delimited: Research carried out in humans that specifically evaluated the possible effects of CBD, studies that addressed some type of mental disorder, and the study should be a double-blind randomized clinical trial.

Articles that presented an approach outside the guiding question and/or that evaluated without a placebo control group were excluded; as well as the articles that were in duplicate.

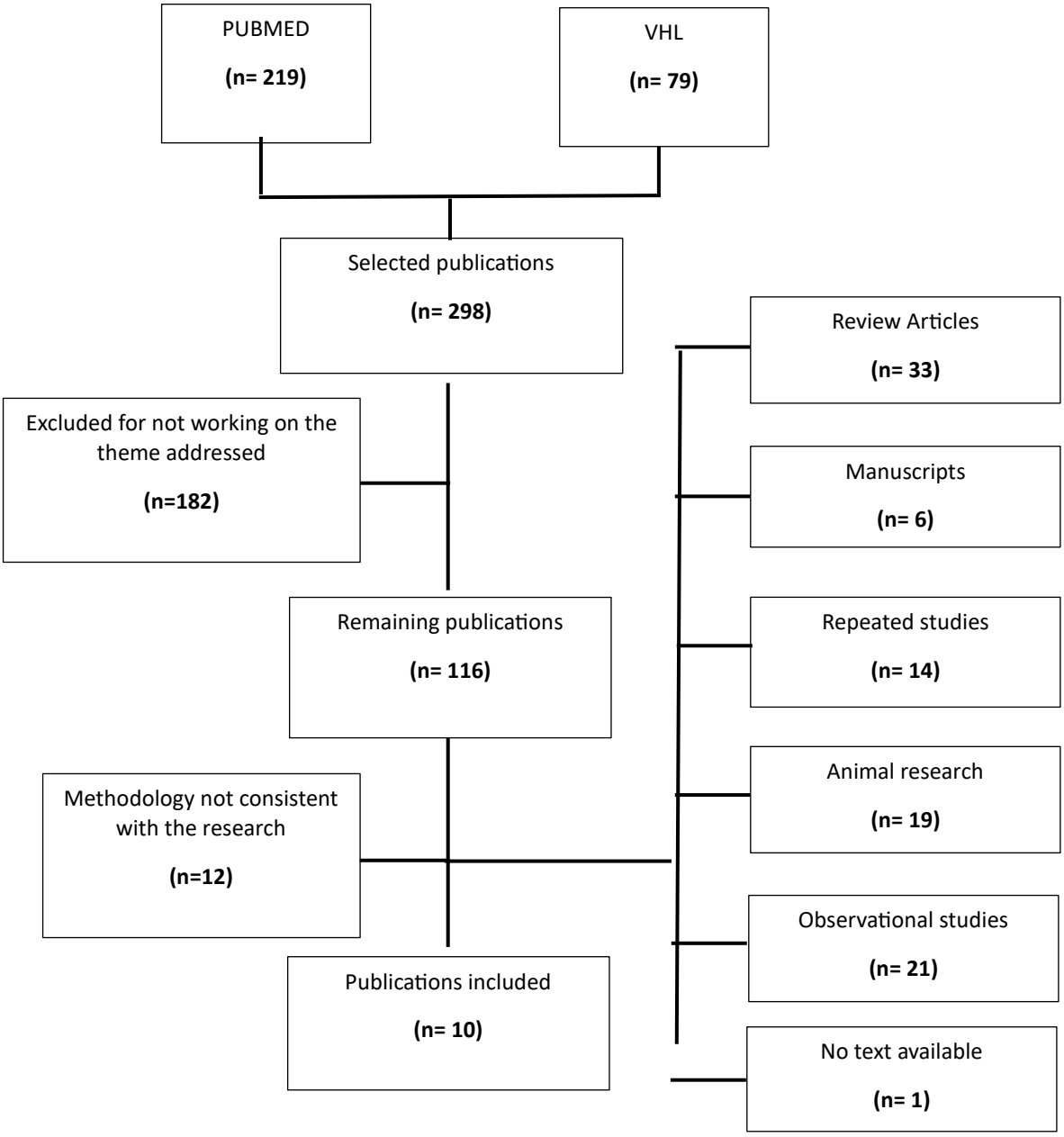
The studies selected for full reading had their methodologies and results analyzed in detail in order to avoid the occurrence of "distorted results", "confusion" and "random occurrence". To determine the value of the study, the following questions were answered: "Were the results biased?"; "Are there confounding or bias factors present or lack of standardization among study participants?" and "Is there a possibility that the results came about by chance?" "YES" and "NO" answers were given. If the answers were NO to the three questions, the research was considered reliable with a low risk of bias.

The level of evidence was determined using GRADE (Grading of Recommendations Assessment, development and Evoluation). From this tool, the quality of the evidence and the strength of the recommendations of the pharmacological protocol can be graded. GRADE has four levels of evidence: very low, low, moderate and high; which depend on whether issues such as risk of bias, inconsistency, inaccuracy, and publication bias are serious, very serious, or not serious.

RESULTS AND DISCUSSION

After searching the databases, following the previously mentioned strategy, 298 articles were found, 219 from PubMed and 79 from the VHL, however, after reading the abstracts, only 10 articles were selected for complete reading, as described in figure 1.

Figure 1 – PRISMA flowchart.



SOURCE: Authorship, 2022.

From the information presented in figure 1, it is necessary to present a table with clarifications about the 10 articles included in this review.

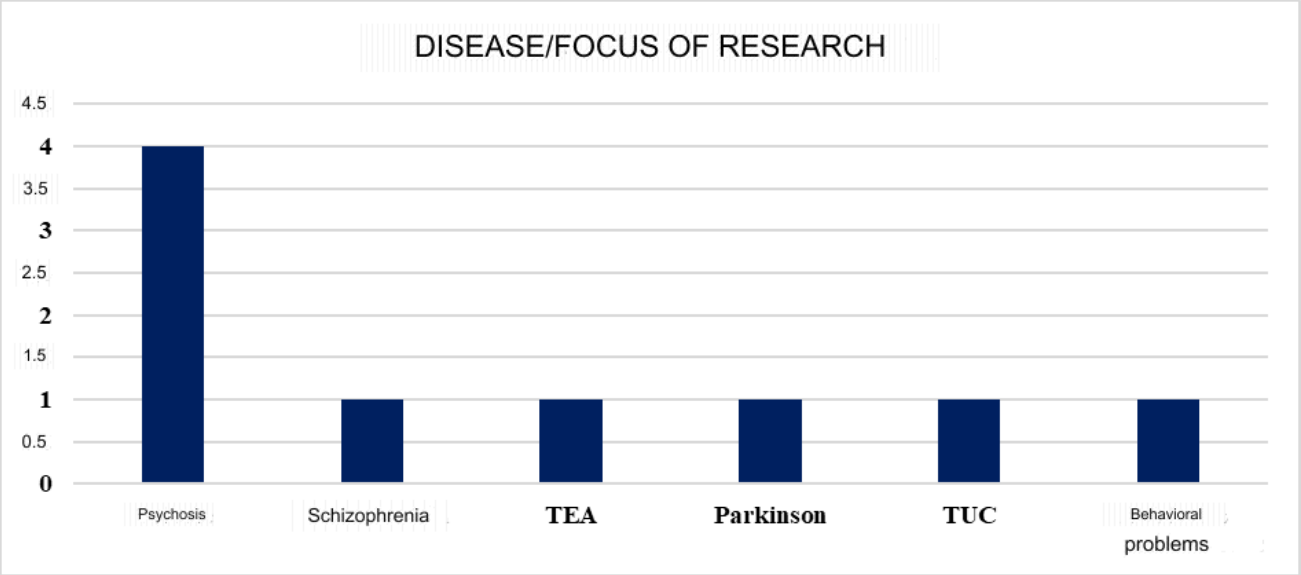
Chart 1 – Characterization of the articles in the bibliographic sample.

Study	Title	Newspaper	Authors/Year
E1	Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study.	Depress Anxiety	KAYSER, R.R. et al, 2020
E2	A pilot randomised placebo-controlled trial of cannabidiol to reduce severe behavioural problems in children and adolescents with intellectual disability.	Br J Clin Pharmacol	EFRON D. et al, 2020
E3	A single dose of cannabidiol modulates medial temporal and striatal function during fear processing in people at clinical high risk for psychosis	Transl Psychiatry	DAVIES C. et al, 2020
E4	Cannabidiol and Amisulpride Improve Cognition in Acute Schizophrenia in an Explorative, Double-Blind, Active-Controlled, Randomized Clinical Trial.	Front Pharmacol	LEWEKE, F.M. et al, 2021
E5	Cannabidiol for Rapid Eye Movement Sleep Behavior Disorder.	Mov Disord	DE ALMEIDA, C.M.O. et al, 2021
E6	Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial.	Lancet Psychiatry	FREEMAN, T.P. et al, 2020
E7	Cannabidiol modulation of hippocampal glutamate in early psychosis	J Psychopharmacol	O'´NEILL A, et al, 2021
E8	Cannabinoid treatment for autism: a proof-of-concept randomized trial.	Mol Autism	ARAN, A. et al, 2021
E9	Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis.	Psychopharmacology (Berl)	APPIAH-KUSI E. et al, 2020
E10	Normalization of mediotemporal and prefrontal activity, and mediotemporal-striatal connectivity, may underlie antipsychotic effects of cannabidiol in psychosis.	Phychol Med	O'´NEILL A, et al, 2021

SOURCE: Authorship, 2022.

The information extracted from the publications included in chart 1 was organized into 6 categories to better structure the results found about the possible therapeutic uses of Cannabidiol (CBD) in the treatment of each mental disorder analyzed: Psychosis, Schizophrenia, Autism Spectrum Disorder (ASD), Cannabis Use Disorder (TUC), Behavioral Disorders and Parkinson's Disease.

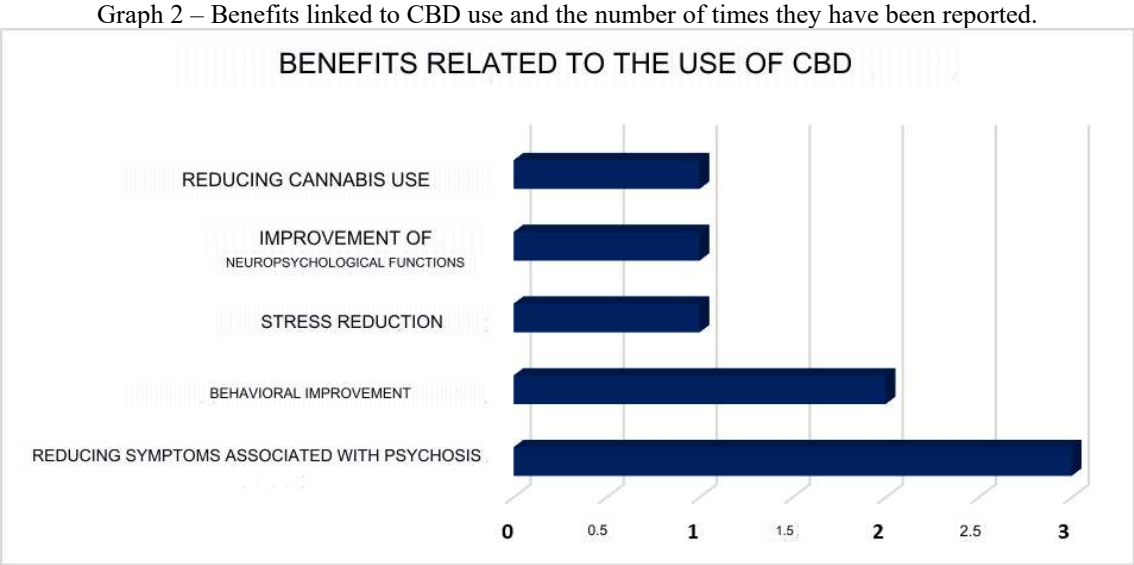
Graph 1 - Relationship between the number of studies and their diseases/research focuses



SOURCE: Authorship, 2022.

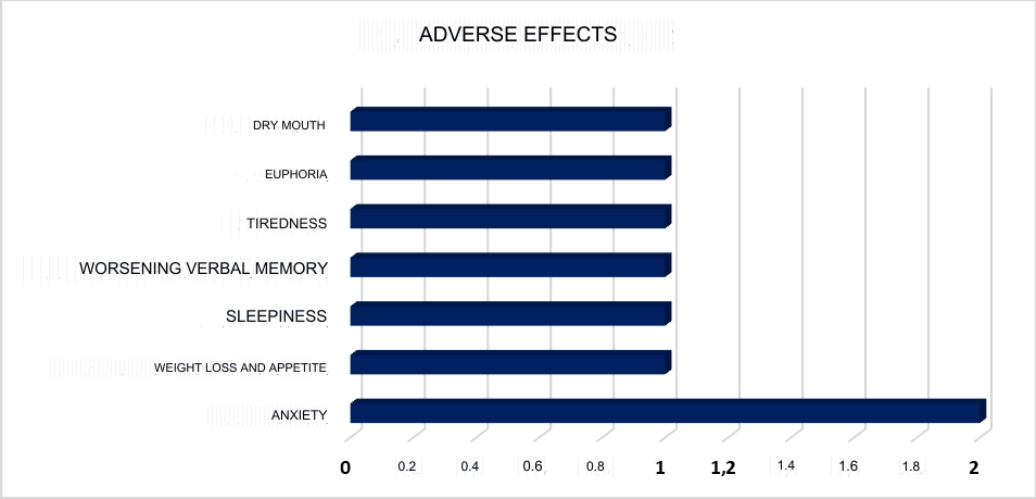
In an overview, the main benefits and adverse effects found from the use of CBD as a therapeutic tool for the management of mental illnesses will be presented in a visual way, with the aim of synthesizing the main findings of the present study.

Graph 2 – Benefits linked to CBD use and the number of times they have been reported.



SOURCE: Authorship, 2022.

Graph 3 – Adverse effects associated with CBD use and the number of times they were described.



SOURCE: Authorship, 2022.

USE OF CBD FOR TREATMENT OF PSYCHOSES

All studies that have addressed the effects of CBD in the treatment of psychoses have shown promising results, indicating that CBD can have positive and relevant effects on this disease, especially if administered in the early stages (BATALLA et al., 2019).

In these studies, a significant improvement in the severity of psychosis symptoms was observed, so that CBD treatment appeared to partially normalize the connectivity and activation of specific brain regions involved in the psychopathology of psychoses. Thus, the current studies present in the literature suggest that psychoses originate from a spontaneous increase in dopamine on reward pathways, leading to abnormal stimulation of reinforcement actions, so the probable effect of CBD would be to act on these same processing pathways in the opposite way (Gunasekera; Dideren; Bhattacharya, 2022).

In this context, studies have shown that CBD also had a relevant influence on the modulation of other processes in the brain, such as the act of remembering (memory), cognition, and the perception of fear. This is through the promotion of greater or lesser activation of specific areas of the brain (BATALLA et al, 2021). However, such effects depend on some factors such as: The dosage used; The route of use; The progression of the disease (acute or chronic case); And the presence of other associated comorbidities (DAVIES; BHATTACHARYYA, 2019).

More specifically, in E3, E7 and E10, it was pointed out, that CBD altered glutamate levels and/or arousal in the left hippocampal region when compared to the group receiving placebo. In addition, in other areas/groupings of the brain such as the right parahippocampal gyrus, left middle frontal gyrus, left amygdala, putamen and caudate nucleus were also influenced by this drug, so these effects proved to be positive, being associated with an attenuation of the symptoms of these patients (BATALLA et al, 2021).

The means by which there was this influence exerted by the drug on these regions is not yet completely certain, but some possible mechanisms of action have already been reported in the literature, such as: Negative allosteric modulation of CB1/CB2 receptors; Partial agonism of D2 dopaminergic receptors; The inhibition of the hydrolysis of anandamide and the consequent increase in its levels; And stimulation of 5-HT1A receptors (CHESNEY; OLIVER; MCGUIRE, 2022; GARCÍA-GUTIÉRREZ et al., 2020; GUNASEKERA; DIEDEREN; BHATTACHARYYA, 2022).

In addition, in E9, a relationship was observed between the use of CBD and stress associated with a change in cortisol levels and its reactivity in those patients, as well as a relationship with anxiety, identified through the STAI-S AUC assessment. In this work, the positive action of this drug in relation to stress and anxiety was clear, where the substance showed intermediate results when compared to the healthy group and the placebo.

In most of the articles, a linear relationship was observed between the groups studied, so that the control group had better results in the tests selected by the research and the one treated with placebo had worse evaluations, while the group receiving CBD had intermediate evaluations.

USE OF CBD FOR TREATMENT OF SCHIZOPHRENIA

According to E4, patients treated with CBD have been shown to have a considerable improvement in brain activity, especially in their processing speed, visual memory, visual and motor coordination, and the ability to maintain attention. These results were obtained through the ROFT, Digit-Symbol, Trail Making Test B and Continuous Performance Test-Symbol tests. In addition, it is important to highlight that the antipsychotic effects of CBD can be considered in the treatment of schizophrenia (SILVA, 2020).

However, it is worth noting that other studies already available in the literature that compared the treatments usually used for schizophrenia with CBD-based treatments, showed little or even no significant therapeutic difference (GHABRASH et al., 2020; KOPELLI et al., 2020; LEWEKE et al., 2012).

Therefore, in general, the results obtained indicate that the use of CBD is still a big unknown. Since this drug can be considered beneficial in relation to neurocognitive functioning, it can bring benefits to patients with schizophrenia, so the search for its effects on these patients is important to be explored (PATEL, 2020). In addition, it is important to note that the little description of adverse effects associated with this substance means that it may become an alternative treatment option for this disease in the future (HUESTIS, 2019).

USE OF CBD FOR THE TREATMENT OF AUTISM SPECTRUM DISORDER (ASD)

Study E8 showed indications that treatment with cannabinoids can improve the main symptoms of ASD such as: Self-mutilation, anger, hyperactivity, anxiety, irritability, aggressiveness, reduced cognitive abilities, attention problems and depression. These results are supported by the existing literature (ARAN et al., 2019; BARCHEL et al., 2018; BAR-LEV SCHLEIDER et al., 2019; LOSS et al., 2020; SILVA et al., 2022).

It was demonstrated that treatment with cannabinoids has the potential to decrease disruptive behaviors associated with ASD with acceptable tolerance, these results were obtained through positive responses in the Clinical Global Impression (CGI-I) and Social Responsiveness Scale (SRS-2) assessments (BARCHEL et al., 2018). One of the side effects observed was weight loss/BMI concomitant with the use of these substances. And the most prevalent adverse effect observed was drowsiness. Thus, the use of CBD should be explored as a future treatment of symptoms derived from ASD (ARAUJO; TJOA; SAIJO, 2019; LOSS et al., 2020).

USE OF CBD FOR TREATMENT OF BEHAVIORAL PROBLEMS

E2 showed significant clinical improvement (which was defined by the study as the reduction of 1 or more behavioral deviations/ABC-I normative sample assessment) was observed in all three participants using CBD treatment compared to no changes observed in the placebo group (4 subjects), indicating that there was indeed a clinically relevant behavioral change due to the use of this drug.

E1 showed that over time there was an overall decrease in OCD and anxiety symptoms in all groups. However, the use of Tetrahydorcannabidiol (THC) and CBD have been shown to have a negligible effect on these changes in OCD and anxiety manifestations when compared to placebo effects, so that, immediately after placebo administration, a greater reduction in anxiety status (self-reported by the STAI-S assessment) was observed when compared to THC and CBD compounds, and this difference between groups persisted for at least 40 minutes. However, after 60 minutes, this difference was not observed or proved to be irrelevant.

Thus, E1 showed that the constituents of cannabis, THC and CBD, had no influence on the effective treatment of anxiety or OCD symptoms, while E2 showed significant clinical improvement in behavioral disorders from the use of CBD.

Studies such as ARAN, A. et al (2019), show the effectiveness exposed by E2. In it, children with severe behavioral problems were treated. The main adverse effects include sleep disturbances and loss of appetite, however, behavioral outbreaks improved with a high degree of satisfaction in 61% of the study population. These data prove the need for caution on the part of physicians in the

use of CBD for the treatment of behavioral problems, as there are contradictions about the effectiveness of this drug in the treatment of these disorders in the current literature.

USE OF CBD FOR TREATMENT OF CANNABIS USE DISORDER (TUC)

In light of this, it was found that FREEMAN, T. P. et al (2020), tested the use of CBD for the treatment of Cannabis Use Disorder (OCD) in different concentrations (200, 400 and 800 mg).

At 200 mg, the use of CBD proved ineffective. At 400 mg, CBD decreased the number of cigarettes smoked per week during treatment and until the end of observation. However, as an adverse effect, there was a worsening in the quality of sleep in this group. Finally, the use of 800mg of CBD reduced the results of the cannabis abandonment scale during treatment until the end of follow-up, indicating a reduction in symptoms related to cannabis withdrawal. In addition, CBD 800mg reduced anxiety ratings during treatment, showing that this drug is associated with an improvement in these symptoms.

Thus, it is concluded that the use of cannabidiol (CBD), a non-psychotropic phytocannabinoid, is capable – if used in certain concentrations – of reducing the psychotropic effects of the other substances present in *Cannabis sativa.* However, as it is the result of a study, its use should be controlled and more research on the subject should be carried out, with the intention of expanding scientific knowledge on the subject.

USE OF CBD FOR TREATMENT OF PARKINSON'S DISEASE (PD) SYMPTOMS

Regarding the symptoms of Parkinson's disease, study E5 observed that the daily use of 300mg of CBD over a 12-week period was not enough to reduce RBD/REM manifestations, nor did it produce a significant improvement over CGI when compared to the use of placebo.

Since, the analysis of variance between the placebo group and the one that underwent the CBD intervention showed no interaction/change on the severity (CGI-S) and improvement (CGI-I) sub-items, proving that this drug (AND placebo) did not present any statistically relevant effect.

However, it is worth noting that a greater satisfaction of the CBD group was observed when compared to the control group in relation to sleep during the fourth and eighth week of treatment.

Study E5 showed no relevant effect of the use of cannabinoids for the treatment of Parkinson's Disease (COORAY; GUPTA; SUPHIOGLU, 2020). However, it demonstrates the risk of misuse of this drug, since neurotoxicity was found from the indiscriminate use of this therapy, which demonstrates the need to control herbal measures based on these substances.

However, PATRÍCIO, F; et al, 2020, demonstrates that cannabinoids can act by activating dopaminergic receptors of the CB1, CB2 and TRPV-1 types, which will act in the pathways of the basal ganglia (where Parkinson's Disease develops). Thus, it is understood that the activation of these

receptors can have neurocompensatory, neuromodulatory and neuroprotective effects, being positive in the treatment of the disease. Thus, it is concluded that there is a need for more conclusive studies on the use of CBD for the treatment of PD and its use should be controlled by health professionals, in order to avoid negative effects of its use in patients.

CONCLUSION

The therapeutic effects of CBD are not yet fully known, however several studies have already proven that this drug has the ability to modulate key regions of the brain associated with mental disorders. Thus, the effectiveness of its use in the treatment of psychotic patients and those with autism spectrum disorder showed very promising results.

Thus, this brain modulation made by CBD seems, in these pathologies, to act by reducing aggressive behaviors, irritability, hyperactivity of individuals, with a concomitant functional improvement of cognitive processes and social interaction.

In addition, something that should be emphasized is that this drug is well tolerated by the body and therefore does not generate a wide variety of adverse effects, being an advantage over other antipsychotic drugs currently available (HUESTIS, 2019; BATALLA, 2021). Another major difference between CBD and current antipsychotics is that CBD does not act through dopaminergic pathways. Therefore, it is possible that this drug is the beginning of a new class of antipsychotics, representing great advances in this area (CHESNEY; OLIVER; MCGUIRE, 2022).

However, it is clear that the number of large-population studies involving CBD is scarce. Therefore, it is essential to carry out broad clinical trials that demonstrate with more quality and specificity the pharmacological performance of this drug, proving or not its real therapeutic effectiveness.

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