Antidepressant-Like and Anxiolytic-Like Effects of Cannabidiol: A Chemical Compound of *Cannabis sativa*

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Abstract: Anxiety and depression are pathologies that affect human beings in many aspects of life, including social life, productivity and health. Cannabidiol (CBD) is a constituent non-psychotomimetic of *Cannabis sativa* with great psychiatric potential, including uses as an antidepressant-like and anxiolytic-like compound. The aim of this study is to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound. Studies involving animal models, performing a variety of experiments on the above-mentioned disorders, such as the forced swimming test (FST), elevated plus maze (EPM) and Vogel conflict test (VCT), suggest that CBD exhibited an anti-anxiety and anti-depressant effects in animal models discussed. Experiments with CBD demonstrated non-activation of neuroreceptors CB1 and CB2. Most of the studies demonstrated a good interaction between CBD and the 5-HT1A neuro-receptor.

Keywords: Anxiety, anxiolytic-like, cannabis sativa, cannabidiol, CBD, major depression.

INTRODUCTION

Anxiety can be defined as a vague and unpleasant feeling that can be compared to fear or apprehension and that is usually caused by anticipation of a risk, danger or unknown situation [1, 2]. Anxiety and fear are considered pathological from the moment they become exaggerated, irrational and dysfunctional with regard to the stimulus, as well as when they begin to interfere in the daily activities of the subject, reducing their quality of life and performance in daily life activities [1]. Other factors differentiating between normal and pathological anxiety are the duration of the symptoms, voluntary restraint and whether anxiety occurs on the spur of the moment [3].

Anxiety disorders are clinical situations in which these symptoms appear in isolation and are not associated with any other secondary frame of reference or any other disease [3], although sometimes there is a difficulty in determining which is the primary symptom, because the patient presents with multiple concomitant and comorbid pathologies [4].

Depression can appear on several occasions: as a comorbid psychiatric condition [5] linked to substance abuse, to response to stress, or due to bereavement and clinical conditions, as has been pointed out in several studies [6-10]. It can also occur as a comorbid condition in chronic diseases and in diseases that cause pain, deformity, disability and even reductions in quality of life and life expectancy.

Depressed patients present symptoms such as mood changes, apathy, lack of ability to feel pleasure (anhedonia), increased levels of irritability, prostration, cognitive and psychomotor changes and changes in appetite and sleep regimen, among others. They can manifest themselves in different ways, but are often considered as a part of cyclothymia, as a characteristic of bipolar disorder types I and II, as major depressive disorder, as dysthymia and as melancholy [5].

Cannabis sativa is among the most commonly used drugs in the world, with approximately 20% of young people having used this drug [11]. It contains more than 400 different compounds, of which 66 are named phytocannabinoids [12]. Delta 9 tetrahydrocannabinol (THC) is the major active chemical component of this plant and the main ingredient responsible for the hallucinogenic effects of the consumed plant. Cannabidiol (CBD) is the second major active chemical compound [13] in the plant, and it has a large structure (Fig. **1**). This compound has been studied for more than three decades, and in this period, many findings were found in anxiety disorders, social phobia, schizophrenia, depression and other psychiatric conditions [14-17].

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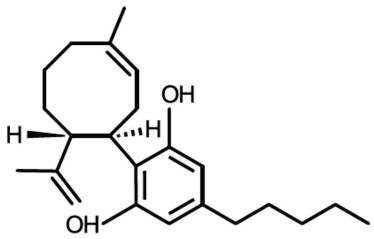

Fig. (1). CBD structure.

Research with animal models is an important step during the investigating process of a particular substance before making it marketable. This step consists in establishing the lethal dose, the half-life and effective and safe dosages. In addition, preclinical research is an important environment for guiding the substance usage.

CBD, different from the main constituent THC, is not hallucinogenic and can be isolated from the others constituents of the *Cannabis sativa* plant. It is a potential psychotherapeutic drug [18]. Thus, the aim of this study is to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound.

METHODOLOGY

We identified articles using the major electronic database, including ISI Web of Knowledge, Scielo, PubMed and PsycINFO. As languages for this search, we used Portuguese and English. We combined the terms "Cannabidiol", "antidepressant-like" and "anxiolytic-like". Thirteen studies were found related to the term "antidepressant-like" on ISI Web of Knowledge, and in the other databases, we only found the same articles. We used five articles as main studies from this search. Using the term "anxiolytic-like", 19 articles in ISI Web of Knowledge, 21 papers in PubMed, two articles in SciELO and nothing in PsycINFO were found; excluding repeated articles among the electronic databases, we took 14 of these articles, which were animal studies of CBD and which met the other criteria described below (Fig. **2**), for this review. Also, five articles suggested by fellows were included.

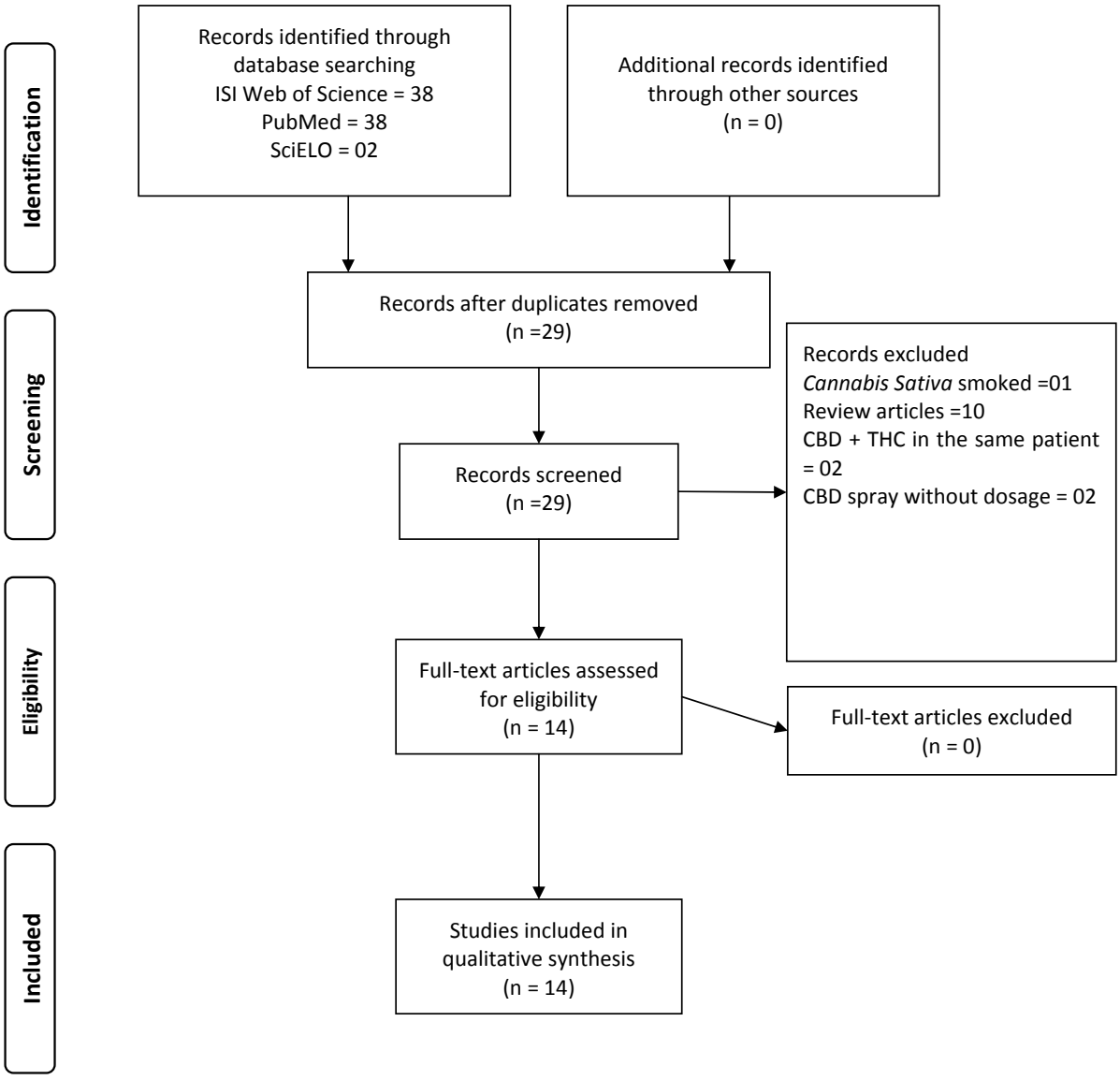

Fig. (2). Results of search strategy related to anxiolytic-like effects of cannabidiol.

This study included animal studies regarding depression or anxiety models, using CBD as an isolated substance. We excluded from this review articles using CBD concomitant with THC on the same animal or that involved smoking of *Cannabis sativa*, as it is impossible to define the dose compositions and proportions of the many different compounds in the plant. Table **1** describes all selected studies.

RESULTS

Antidepressant Effects of CBD

In 1977, Porsolt *et al*. [19] were the first to describe the forced swimming test (FST) as a useful tool in research. It consists of placing a rat in a cylinder full of water, where there is a stand hidden by the water but that is high enough for the rat to stay comfortable without the necessity to swim. In this test the rat is released into the water, and it must swim to stay alive and instinctively to find a way to leave the water. Exploring the cylinder surface, the rat can find the stand. In researches with depressed rats, they stay in the water without moving unlike normal rats, which usually try to find a place to stay.

In 2011 [20], rats were treated with CBD in different doses (15, 30 and 60 mg/kg), imipramine (30 mg/kg) or saline solution as placebo. This research showed that CBD in the 30 mg/kg dosage had similar effects to imipramine, with a larger number of rats climbing compared to rats treated with saline solution and slightly higher numbers of rats that received other dosages of CBD. The study also discussed brain-derived neurotrophic factor (BDNF), a biomarker also used to detect depression. In fact, decreased levels of BDNF have been shown in depressed animal and humans [21-23]. Conversely, administration of antidepressant treatments increases BDNF expression [24], and brain infusion of BDNF produces antidepressant-like actions in rats [22, 24]. Compatible with an antidepressant effect, an increase in BDNF was detected in animals treated with CBD, as well as in the animals treated with imipramine.

Other study on animal model [25] was performed using FST and found the same antidepressant-like effect in a dose-dependent manner, and also a non-hallucinogenic effect in rats, unlike the rats that received THC.

A study using an open field arena [26], with rats treated with CBD, showed interesting results regarding motor activity. Animals received injectable doses of CDB (i.e., 3, 10, 30 and 100 mg/kg) and placed in a circular open field arena (40 cm in diameter with a 50-cm-high Plexiglas wall), in which exploratory activity was videotaped for 6 min. Results showed decreased activity over the time of exposure, but it was not correlated with any dose of CBD, since the control animals behavior remained the same. The findings agree with the data of Guimarães *et al*. [27], indicating that CBD does not induce significant motor changes; the antidepressant-like effect of CDB is not secondary. In addition [27], authors also used FST adding the variable WAY 100635 (WAY), a 5-HT1A antagonist, and found similar results to other studies published previously. Rats were treated with WAY and received CBD (30 mg/kg^{-1}) or vehicle (placebo) 30 minutes later and then another dose 30 minutes after the first, subsequently to exposition to FST. These results were also compared with other group that received imipramine (30mg/kg^{-1}), and CBD was also effective in the FST, however, the BDNF levels were not modified.

In addition to the expected results related to FST (i.e., rats not treated with WAY), rats that received WAY spent more time only floating, like rats that received placebo (vehicle), clearly demonstrating a "non-effect" of CBD and leading researchers to conclude that the neuroreceptor 5-HT1A participates in the mechanism of action of CBD [26].

An experiment [28] used the Light-dark (LD) immersion model, a test based on the innate aversion of rodents to bright and illuminated areas and on the spontaneous exploratory behavior of the animals. Thus, there is a conflict between the tendency to explore and the initial tendency to avoid the unfamiliar. This test consists of two compartments, the first one is dark and the second one is illuminated. Differently from the results of [27], CBD failed on modifying the rats' responses to the test.

Anxiolytic Effects of CBD

Animal studies are an important way to test a substance before use it in human beings. CBD also has anxiolytic-like activities; therefore, we consider the most important studies that tested CBD in animal models. One way to undertake experiments with anxiety is to use the elevated plus-maze [28], which consists of a maze in a cross form, elevated approximately 50 cm above the floor. It has two arms with protections (walls) and two without walls. In the first experiment we found, mice that received CBD, diazepam or a vehicle (i.e., no active substance or placebo) and placed in the center of the maze, in front of the closed face. The flow rate and input into the arms were measured for 10 minutes.

The results showed that the increase in the frequency of open arm entries by animals that received CBD was statistically significant, compared to the frequency observed in animals that received only vehicle, regardless of the dose used (2.5, 5.0, and 10.0 mg/kg). Also, the use of 20.0 mg/kg of CBD was plotted on a graph in an inverted "U" shape. Low doses led to the rats to explore all of the arms of the maze, suggesting an anxiolytic effect, while higher doses caused a return to the baseline data.

Other experiment [29] using the EPM also resulted in a similar graph to the first study [28], an inverted "U" or bell-shaped curve. These results were obtained using CBD versus vehicle. Later, in other study by the same group [30], CBD administered inside the brain (i.e., right dorsolateral and ventral regions of the periaqueductal gray matter) also increased the percentage of entries into the open arms of the maze, but CBD did not affect the amount of time spent in the open arms. The parameters used were considered significant for measuring anxious behavior. However, these results are often not observed in this type of study.

With respect to the EMP experiments, Hsiao *et al*. [31] conducted an experiment evolving rats in a persistent stress conditioned task using open fields and EPM, with the sleep

Table 1. Main results of studies associated with antidepressant-like and anxiolytic-like effects of cannabidiol.

Ref.	Objective	Methodology	Results	Conclusion
[20]	The main objective of the present study was to evaluate behavioral and molecular effects induced by administration of CBD and imipramine in rats.	Rats treated for 14 days with saline, CBD (15, 30 and 60 mg/kg) or imipramine (30 mg/kg) and the animals behaviour was assessed in forced swimming and open-field tests. BDNF levels were also measured.	We observed that both acute and chronic treatments with imipramine at the dose of 30 mg/kg and CBD at the dose of 30 mg/kg reduced immobility time and increased swimming time. CBD at the dose of 15 mg/kg and imipramine at the dose of 30 mg/kg increased BDNF levels in the rat amygdala.	Results indicate that CBD has an antidepressant-like profile and could be a new pharmacological target for the treatment of major depression.
[25]	This study was conducted to assess the antidepressant-like activity of Cannabinoids.	Cannabinoids were initially evaluated in the mouse tetrad assay to determine doses that do not induce hypothermia or catalepsy. The automated mouse FST and TST tests were used to determine antidepressant action.	CBD exhibited significant effect at 20 and 200 mg/kg, respectively.	Δ9-THC and other cannabinoids exert antidepressant-like actions, and thus may contribute to the overall mood-elevating properties of cannabis.
[26]	The aim of this work was to test the hypothesis that CBD would have antidepressant-like activity in mice as assessed by the FST and investigated if these responses depended on the activation of 5-HT1A receptors and on hippocampal expression of BDNF.	Mice were given CBD (3, 10, 30, 100 mg·kg-1), imipramine (30 mg·kg-1) or vehicle and were submitted to the FST or to an open field arena, 30 min later. An additional group received WAY (0.1 mg·kg-1) a 5-HT1A receptor antagonist, before CBD (30 mg·kg-1).	CBD (30 mg·kg-1) treatment reduced immobility time in the FST. WAY pretreatment blocked CBD-induced effect in the forced swimming test.	CBD induces antidepressant-like effects comparable to those of imipramine. These effects of CBD were probably mediated by activation of 5-HT1A receptors.
[38]	The aim of this study was to further investigate the role of the bed nucleus of the stria terminalis on the anxiolytic effects of the CBD.	Male Wistar rats received injections of CBD (15, 30, or 60 nmol) into the BNST and were exposed to the EPM or to the VCT, two widely used animal models of anxiety.	CBD increased open arms exploration in the EPM as well as the number of punished licks in the VCT, suggesting an anxiolytic-like effect.	These results give further support to the proposal that BNST is involved in the anxiolytic-like effects of CBD observed after systemic administration, probably by facilitating local 5-HT1A receptor-mediated neurotransmission.
[34]	Test the hypothesis that CBD could also impair escape responses evoked by two proposed animal models of panic: the elevated T-maze (ETM) and electric stimulation of dPAG.	Three experiments using the CBD injected into the dPAG.	In the ETM microinjection of CBD into the dPAG impaired inhibitory avoidance acquisition, an anxiolytic-like effect, and inhibited escape response, a panicolytic-like effect. The drug also increased escape electrical threshold, an effect that was prevented by WAY.	Together, the results suggest that CBD causes panicolytic effects in the dPAG by activating 5-HT1A receptors.
[22]	To verify, using c-Fos immunocytochemistry, if the mPFC is involved in the attenuation of contextual fear induced by systemic administration of CBD and investigate if direct microinjections of CBD into mPFC regions would also attenuate contextual fear.	Five experiments involving fear c onditioning and injected CBD in the prelimbic or infralimbic prefrontal cortex.	Systemic administration of CBD decreased contextual fear.	These results suggest that the PL prefrontal cortex may be involved in the attenuation of contextual fear induced by systemic injection of CBD.
[36]	The aim of the present work was to test the hypothesis that CBD would attenuate the autonomic and behavioral consequences of restraint stress.	Rats received i.p. injections of vehicle or CBD and 30 min later were submitted to 60 min of restraint where their cardiovascular responses were recorded.	Exposure to RS increased blood pressure and heart rate and induced an anxiogenic response in the EPM 24h later.	The results suggest that CBD can attenuate acute autonomic responses to stress and its delayed emotional consequences by facilitating 5-HT1A receptor-mediated neurotransmission.
[30]	Test the hypothesis that, at high doses, cannabidiol and WIN 55,212-2 could activate TRPV1 receptors.	Rats with cannulae placed in dlPA G underwent three treatments, involving CBD and EPM.	CBD result showed ansiolitic and was compatible in respect to the expected placebo.	These results suggest that TRPV1 receptors in the dlPAG modulate anxiety.

(Table 1) contd…..

References	Objective	Methodology	Results	Conclusion
[37]	Investigate the central effects of the eCB uptake/metabolism inhibitor AM404 and the phytocannabinoid cannabidiol (CBD) on the extinction of contextual fear memories in rats.	Five experiments involving adult male Wistar rats. Drugs used: AM404, CBD. Capzazepine and diazepam. Tests conducted at EPM.	The result showed ansiolitic and was compatible with diazepam a common used ansiolitic.	CBD, a non-psychoactive phytocannabinoid could be an interesting pharmacological approach to reduce the anxiogenic effects of stress and promote the extinction of fear memories.
[29]	To investigate if the dlPAG could be a possible site of the anxiolytic effects induced by CBD and if these effects depend on CB1 or 5HT1A receptors.	Rats with cannulae aimed at the dlPAG were tested in the EPM and the VCT.	The anxiolytic effect of CBD was confirmed in the VCT. These effects were prevented by WAY.	These results suggest the CBD interacts with 5HT1A receptors to produce anxiolytic effects in the dlPAG.
[33]	The aim of the present study was to test the effects of CBD in the Vogel test, a widely used animal model of anxiety.	Rats were deprived of water for 2 4 hours and placed in the VCT, using CBD, flumazenil or diazepam.	CBD induced an anticonflict effect not mediated by benzodiazepine receptors.	These results reinforce the hypothesis that this cannabinoid has anxiolytic properties.
[35]	The aim of this work was to compare the behavioral and cardiovascular effects of CBD and diazepam in animals submitted to a contextual conditioned fear paradigm.	Rats were conditioned with fear and had their freezing behaviors monitored.	Conditioned rats submitted to the aversive context exhibited more freezing behavior and a larger increase in blood pressure and heart rate as compared to non-conditioned animals.	the results suggest that CBD has anxiolytic-like properties similar to those of diazepam in a rat model of conditioned fear to context.
[27]	Assess the presence of anxioliytic proprieties in CBD.	The drug was tested in rats using the elevated plus-maze.	The doses of CDB increased the number of entry in the EPM.	These results indicates that CBD causes selective anxiolytic effect in the EPM.
[39]	The aim of this study was to investigate the effects of cannabidiol on innate fear-related behaviors evoked by a prey *vs* predator paradigm.	Mice were submitted to habituation in an arena containing a burrow and subsequently pre-treated with intraperitoneal administrations of vehicle or cannabidiol. A constrictor snake was placed inside the arena, and defensive and non-defensive behaviors were recorded.	Cannabidiol caused a clear anti-aversive effect, decreasing explosive escape and defensive immobility behaviors outside and inside the burrow.	These results show that cannabidiol modulates defensive behaviors evoked by the presence of threatening stimuli, even in a potentially safe environment following a fear response, suggesting a panicolytic effect.

CBD: Cannabidiol; BDNF: Brain-derived neurotrophic factor; WAY: WAY 100635; TST: Tail suspension test; EPM: Elevated plus-maze; VCT: Voguel conflict test; FST: Forced swimming test; dlPAG: Dorsolateral periaqueductal gray; dPAG: Dorsal periaqueductal gray.

regulation context, showed that rats treated with CBD, reduced the number of entries on the field with protection and spent more time on the open arms and on the center. CBD blocked efficiently anxiety and induced rapid eyes movement (REM) sleep suppression, but had little effect on non-REM sleep.

A variation of EPM, i.e. the elevated "T" maze (ETM), was used in an experiment [32] to study the role of the serotoninergic neurotransmission in the DPAG, on response modulation of escapes. This showed that peripheral administration of CBD decreases the escape in the ETM, suggesting a panic lytic effect. Once the mentioned effects of CBD were prevented by the use of the 5-HT1A receptor agonist, researchers suggested that the repeated treatment with the substance may prevent panic like attacks.

In an experiment [33] using the Vogel Conflict Test (VCT), a test that places rats in a conflicted situation, a water-deprived animal is put in a cage with a floor grid and is offered water. However, after the rat laps the water a certain number of times predetermined by the researcher, rat receives a shock on the tongue. Thus, the rat experiences a conflict between the need for water and fear of punishment. Three substances were injected into the rats: CBD (multiple doses of 2.5, 5 and 10 mg/Kg), diazepam (i.e., a proven anxiolytic), and either flumazenil (i.e., a benzodiazepine receptor antagonist) or vehicle (i.e., no active drug or placebo). The tests showed that CBD had an effect consistent with diazepam effects, increasing the number of licks, including those that resulted in punishment. The administration of diazepam plus flumazenil resulted in a reduced anxiolytic effect, which did not occur as a result of a combination of CBD and flumazenil.

Moreover, two experiments [29, 34] involving the injection of WAY directly into the dorsolateral portion of the periaqueductal gray matter (dlPAG) of rats demonstrated that WAY has affinity with CBD. Authors found a similar conclusion in a study that administered WAY11 to mice in the EPM, but it was not injected directly into their dlPAG.

Other study [35] aimed to examine cardiovascular and behavioral responses in situations of contextual fear. Authors used the foot shock cage, which is made of Perspex walls and a grid formed by stainless steel rods (typically 25 cm x 22 cm x 22 cm). Mice have certain time to explore the cage, after this time, the grid delivers shocks to the foot of the animal at a time frequency and intensity determined by the controller. It is generally used to condition mice. This "fear conditioning" experiment used mice preconditioned to a hostile environment (foot shocks) and a control group, which interacted with a non-hostile environment. The drugs used in the experiment were CBD, diazepam, vehicle, and FG-7142, an inverse agonist of the benzodiazepine receptor.

The results showed that "freezing" behavior was very low in animals that were not conditioned to fear (i.e., less than 20% of the time of animals that received vehicle). For the conditioned mice, diazepam reduced freezing more than vehicle or FG-7142. In addition, not only the preconditioned mice but also the control groups (treated with FG-7142), produced a small but significant reduction in freezing behavior.

Regarding the impact of cardiovascular disease, there were small changes among the non-conditioned rats in either blood pressure or heart rate. However, in conditioned rats, the assessments of those animals treated only with vehicle or FG-7142 modified, and CBD and diazepam stabilized and even succeeded in reducing both the heart rate and blood pressure of the tested rats. Researchers concluded that the study's results were consistent with experiments using CBD plus diazepam.

A further demonstration of the anxiolytic effect of CBD on cardiovascular data [36] was obtained in a study that animals were exposed in the EPM to different doses of CBD and compared their activity to those that received vehicle (as a control) and the antagonist WAY, which works on 5-HT1A neuroreceptors. CBD reduced the tachycardia response to residual "stress", attenuating an increase in anxiety, although these effects were blocked by WAY.

Contextual fear was also used in experiments with CBD, together with substances tested for the inhibition of neural receptors (AM404, capsazepine [CPZ], and SR141716A [SR]) and with diazepam [37]. Rats were placed in boxes that, after three minutes, they received shocks lasting one second after being kept in place for 1 minute, until they returned to their cages. Freezing behavior was observed. This type of conditioning was also used in the EPM experiments.

The results once again demonstrated the effectiveness of CBD as an anxiolytic drug compared with diazepam. AM404 was also effective in diminishing the effects of fear preconditioning. Such responses were antagonized by the selective CB1 agonist SR, but they were not antagonized by the TRPV1 agonist CPZ. Regarding contextual fear conditioning, the prefrontal cortex (PFC), which received systematically CBD, has been shown to be involved in mitigating the effects of fear [27].

With the purpose of demonstrating that the TRPV1 receptors in the dlPAG matter mitigate the anxiolytic effects of cannabinoids, an experiment [24] with rats and EPM tested this hypothesis using CBD, analyzing the TRPV1 receptor antagonist CPZ and CB1 receptor agonist WIN 55.212-2 mesylate (WIN). The receptors were injected into dlPAG. Again, CBD increased the percentage of entries into the EPM, but the group that received only CPZ was not different from the group that received vehicle. With regard to the effects of WIN, higher doses (i.e., an intermediate dosage was the most effective) had opposite results to the effects of vehicle. Finally, compared with WIN, CPZ affected the number of entries into the open arms of the EPM; rare among rats previously treated with CBD, the percentage of entries into the open arms of the EPM increased when CBD was combined with CPZ.

Finally, a study published in 2011 linked anxiolytic effects to CBD that was injected into the "bed nucleus of the stria terminal" (BNST) [38]. Animals received various doses of CBD (15, 30, 60 n mol) intra-BNST and were exposed to the EPM or the VCT. Results demonstrated that the number of punishment-inducing licks in the VCT and the number of entries into the open arms of the EPM increased when CBD was used. However, the effects of CBD were blocked in rats pretreated with WAY.

In 2011, other experiment was performed on the anti-aversive effects of CBD on innate fear-induced behaviors [39]. Using mice and snakes, researchers put the mice in the arena three days before the experiment and maintained them there with free access to food or water until the day of the experiment.

The "no threat" group was removed from the arena, and their behaviors were recorded (one at a time) for 5 minutes. The remaining animals were exposed to the predator and divided into four groups (n=11-12 per group), which were pre-treated with intraperitoneal CBD (at doses of 0.3, 3, or 30 mg/kg), and a control group, which was administered vehicle.

The group of animals that was not exposed to a confrontation with a wild snake but only to the polygonal arena did not exhibit any defense-like behaviors. However, when exposed to the predator in the same context after 3 days of habituation, all of the mice exhibited defensive behaviors. Sometimes, threatened animals would run to the burrow during confrontation with the predator. Mice pretreated with CBD showed a significant and robust reduction in explosive escape and defensive immobility; these are responses that are considered panic-like behaviors. The response of active avoidance, in which mouse reacts with vigorous movement to avoid close contact with the predator, indicates reduced fear. Risk assessment and defensive attention were unchanged in the animals that received CBD. These findings suggest that CBD decreases the behavioral responses associated with settings of imminent danger, in which the aversive connotation of the stimulus, has been fully recognized.

DISCUSSION

Here, we aimed to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound.

CBD has proved to be a useful and versatile substance, as well as being safe, with an effective dosage that is far from the lethal dose [40, 41]. According to the experiments, CBD did not affect the cognitive functioning or mobility of rats. In prey and predator experiments, animals treated with CBD froze fewer times when exposed to dangerous situations, allowing them to escape from the situation.

Other issue that demands attention deals with the neural receptors responsible for the effects of CBD. The findings of different experiments have yielded conflicting results; for example, one study [34] demonstrated no clear interaction between CBD and the 5-HT1A neuroreceptor, but other studies [29, 35, 38, 42] showed some interaction between them. Perhaps the use of several antagonist substances (e.g.,

WAY and flumazenil) was the major factor responsible for this discrepancy in results.

In addition to 5-HT1A [34, 43], changes in endocannabinoid mediated neurotransmission could also be involved in the effects of CBD chronic administration. Cannabinoids can modulate not only serotonergic neurotransmission, but also the expression of serotonin subtypes 1A and 2A/2C receptors in the brain.

Experiments with depressed rats and CBD showed an increase in rats' movements, an interesting result since authors only expected rats floating in the water, such as depressed rats do. BD also increased BDNF levels in experiments with rats, demonstrating antidepressant-like actions.

The experiment of Hsiao *et al*. [31], using the sleep regulation, demonstrated that CBD blocked the anxiety-induced REM sleep, probably blocking the anxiolytic effect less than the sleep regulation in fact.

Results [26] were also obtained in a dose dependent manner and had similar results compared with market antidepressants. However, the antidepressant failed to change the BDNF levels, and was not found to correlate between the BNDF levels and immobility on the animal. The study of Hsiao *et al*. [28], examined a very low dose of CBD in LD, and does not find the expected results. Previous findings demonstrated an inverse U shape on the effectiveness of CBD, i.e., low doses and high doses had poor results, which may have happened in that experiment.

CONCLUSION

In conclusion, more studies are necessary using CBD as an antidepressant-like drug to better understand its mechanisms of action. However, the results have been very promising, and we can conclude that CBD can become a new drug for the treatment of psychiatric disorders.

LIST OF ABBREVIATIONS

BDNF = Brain-derived neurotrophic factor

BNST = Bed nucleus of the stria terminal

CBD = Cannabidiol

CPZ = Capsazepine

dlPAG = Dorsolateral periaqueductal gray

dPAG = Dorsal periaqueductal gray

EPM = Elevated plus-maze

ETM = Elevated "T" Maze

FST = Forced swimming test

LD = Light-dark

PFC = Prefrontal cortex

REM = Rapid Eyes Movement

SR = SR141716A

THC = tetrahydrocannabinol

TST = Tail suspension test

VCT = Voguel conflict test

WAY = WAY 100635

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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ARTICLE

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug

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DESCRIPTORS
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Abstract
Objectives: To review and describe studies of the non-psychotomimetic constituent of *Cannabis sativa,* cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action. *Method:* The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints. *Results:* Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder. *Conclusion:* Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

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Introduction

Cannabis sativa is the most used drug of abuse worldwide and around 20% of youth use it heavily and regularly around the globe.[1] The main psychoactive component of the plant is Δ9-tetrahydrocannabinol (Δ9-THC), one of the substances responsible for the psychoactive effects of Cannabis.[2-4]

Cannabidiol (CBD) is another abundant compound in *Cannabis sativa*, constituting around 40% of the plant's active substances.[5] The pharmacological effects of CBD are different and often opposite to those of Δ9-THC.[6] The number of publications on CBD has increased remarkably over the last years and support the view that CBD has a vast array of possible therapeutic effects. Among these possibilities, the anxiolytic and antipsychotic properties of CBD stand out.[7-10] CBD's anxiolytic effects are apparently similar to those of approved drugs to treat anxiety,[11] although its effective doses have not been clearly established and the mechanisms underlying these effects are not fully understood. The low affinity of CBD for cannabinoid neuroreceptors[12,13] and its agonist properties at 5-HT1A receptors[14,15] have been repeatedly demonstrated.

Most studies on CBD have been conducted with rodents, but studies with human samples have also provided promising results.[16,17] Therefore, the aim of this paper is to review the scientific literature on the anxiolytic properties of CBD in animal and in humans.

Method

The articles selected for this review were identified by searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". In addition, the reference lists of the selected articles and relevant literature reviews and book chapters were handsearched for additional references. We included experimental studies with human and animal samples with no time limits. We sought to exclude studies that used smoked Cannabis, as it is not possible to establish the dose, composition, and proportion of the different cannabinoids in this case, besides the great individual variations in the samples enrolled. Finally, we did not include studies using extracts containing both THC and CBD in oral (Cannador®) or oromucosal spray (Sativex®) forms due to the difficulty to establish the effects of CBD alone (Table 1).

Animal studies

The two first articles about the effects of CBD on experimental anxiety were published in journals that were not indexed in the databases used for this review but were located through handsearch in the reference lists of relevant literature. These two investigations showed contradictory results. In one study, no significant effects of high doses of CBD (100 mg/kg) were seen in rats in the Geller-Seifter conflict test.[18] In the other, a low dose of CBD (10 mg/kg) had anxiolytic effects in rats submitted to the conditioned emotional response test.[19]

Later studies using the elevated plus maze (EPM) helped to elucidate this contradiction.[9] The EPM consists of two opposing open arms (50 x 10 cm) and two closed arms (50 x 10 x 40 cm) that intersect in their central portion. The arms are made of wood and stand 50 cm above the ground. In this study, mice injected with CBD, diazepam or vehicle (no active substances) were placed in the center of the maze facing the closed arms. The time spent and the numbers of entries in the open and closed arms were measured for 10 minutes. The frequency of entries in the open arms of animals receiving CBD presented an inverted U-shaped curve, with significantly higher rates than those observed in animals treated with vehicle, at the doses of 2.5, 5, and 10 mg/kg. The measures of mice treated with CBD 20 mg/kg did not differ from those of controls, suggesting that anxiolytic effects are only present at low doses, which explains the absence of effects with CBD 100 mg/kg reported in 1981.[18] The same inverted U-shaped dose-response curve was obtained with a wider range of doses of CBD in the EPM (Onaivi et al.).[20] Furthermore, the same pattern was observed with the direct infusion of CBD in the periaqueductal gray (PAG) of rats tested in the EPM,[15,21] confirming that anxiolytic effects should only be expected with low doses of CBD.

The mechanisms through which CBD acts to diminish anxiety have been studied in a number of animal models of anxiety using rodents. One of these studies used Vogel's conflict test,[22] in which the animal is water-deprived from and placed in a cage with an electrified grid at the bottom through which the animal receives a shock after licking water for a predetermined number of times. Three substances were tested in rats using the following procedure: CBD (2.5, 5 and 10 mg/kg), diazepam, and flumazenil (an antagonist of benzodiazepine receptors), in addition to vehicle (placebo). The tests showed that CBD produced effects consistent with those of diazepam by increasing the number of licks, even if they resulted in punishment. Flumazenil antagonized the anxiolytic effect of diazepam, but not that of CBD, suggesting that the effects of CBD are not mediated by the activation of benzodiazepine receptors.

There is strong evidence showing that the serotonergic system is involved in the anxiolytic action of CBD. The injection of the 5-HT1A receptor antagonist WAY-100635 (WAY) directly into the dorsolateral portion of the PAG (dlPAG) in rats antagonized the anxiolytic effects of CBD in the EPM and in Vogel's conflict test.[15] The participation of 5-HT1A receptors in the anxiolytic action of CBD was also derived from behavioral and cardiovascular responses to restraint stress in rats.[11] In this study, animals were intraperitoneally injected with vehicle or CBD (1, 10 and 20 mg/kg) and, after 30 minutes, they were restrained for 60 minutes. Immobilization increased blood pressure, heart rate, and anxiety responses in the EPM 24 hours later, and these effects were attenuated by CBD. Pretreatment with WAY blocked the anxiolytic action of CBD. The injection of CBD into the intra-dorsal PAG also blocked panic-like responses in the elevated T-maze (ETM) and flight responses to the electrical stimulation of this area.[23] The ETM has three arms with the same dimensions, two open and one closed, and allows the measure of entrance avoidance in the open arms when the animal is placed in the closed arm, as well as of escape when the animal is placed in the open arm. The panic-like response seen with CBD in the two procedures was antagonized by the previous intra-dlPAG administration of WAY.[22] Chronic oral administration of CBD also had anti-panic effects in the ETM that were neutralized

Table 1 Studies of the anxiolytic effect of cannabidiol in humans and animals

Study	Model	Route	Dose	Anxiolytic effect
Animals				
Silveira Filho et al.[18]	Conflict test	Intraperitoneal	100 mg/kg	–
Zuardi et al.[19]	Conditioned emotional response paradigm	Intraperitoneal	10 mg/kg	+
Onaivi et al.[20]	Elevated plus maze test	Intraperitoneal	0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 50.0 and 100.0 mg/kg	+
Guimarães et al.[9]	Elevated plus maze test	Intraperitoneal	2.5, 5.0, 10.0 and 20.0 mg/kg	+
Moreira et al.[22]	Vogel's conflict test	Intraperitoneal	2.5, 5.0 and 10.0 mg/kg	+
Resstel et al.[10]	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
Campos et al.[15]	Elevated plus maze test and Vogel's conflict test	Intra-dorsal periaqueductal gray		+
Bitencourt et al.[28]	Contextual fear conditioning	i.c.v.	2.0 microg/microl	+
Campos et al.[21]	Elevated plus maze test	Intra-dorsal periaqueductal gray	30 or 60 nmol	+
Resstel et al.[19]	Restraint stress	Intraperitoneal	1, 10 and 20 mg/kg	+
Soares et al.[23]	Elevated T maze	Intra-dorsal periaqueductal gray	15, 30 or 60 nmol	+
Lemos et al.[29]	Contextual fear conditioning	Intraperitoneal and direct microinjection into the PL prefrontal cortex	10 mg/kg (i.p.) and 30 nmol (microinjection into the PL prefrontal cortex)	+
Casarotto et al.[26]	Marble-burying test	Intraperitoneal	15, 30 and 60 mg/kg	+
Gomes et al.[30]	Vogel's conflict test	Intra bed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Deiana et al.[27]	Marble-burying test	Intraperitoneal and oral	120 mg/kg	+
Uribe-Mariño et al.[31]	Prey-predator paradigm	Intraperitoneal	0.3, 3.0 and 30 mg/kg	+
Campos et al.[24]	Elevated T maze	Oral		+
Humans				
Zuardi et al.[7]	Decreased STAI scores elevation induced by THC (healthy volunteers)	Oral	1 mg/kg	+
Zuardi et al.[32]	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	Oral	300 mg	+
Crippa et al.[34]	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	Oral	400 mg	+
Fusar-Poli et al.[35]	Decreased skin conductance fluctuation in task with fearful faces during a fMRI procedure (healthy volunteers)	Oral	600 mg	+
Crippa et al.[17]	Decreased VAS factor anxiety scores before SPECT procedure (social phobia patients)	Oral	400 mg	+
Bergamaschi et al.[33]	Decreased VAS factor anxiety scores after public speaking (social phobia patients)	Oral	600 mg	+

by intra-dlPAG injection of WAY. However, chronic administration of CBD did not change the extracellular concentration of serotonin in the dlPAG or the expression of 5-HT1A or 5-HT2C, indicating that CBD directly activates 5-HT1A receptors.[24] CBD was also found to activate the vanilloid receptor type 1 (TRPV1)[25] and there is evidence that this activation could explain the inverted U-shaped dose-response curve of CBD's anxiolytic effect seen in the EPM. TRPV1 receptors regulate the release of glutamate in the dlPAG and the increased activation of this system would result in increased anxiety. Thus, it has been suggested that elevated doses of CBD in the dlPAG could activate local TRPV1 receptors facilitating the glutamatergic neurotransmission and increasing anxiety.

To test this hypothesis, rats pre-treated with the TRPV1 antagonist capsazepine in the dlPAG were injected with CBD (30 and 60 mg/kg) in the same region and tested in the EPM. The dose of 60 mg/kg CBD, which had no anxiolytic action before, was able to reduce anxiety after pre-treatment with capsazepine, suggesting that the activation of TRPV1 receptors by the higher dose of CBD would counterbalance the anxiolytic effect of CBD produced by the activation of 5-HT1A receptors.[21]

Because serotonin has also been implicated in obsessive-compulsive disorder (OCD), the effects of CBD were tested in mice submitted to the marble-burying test (MBT), an animal model of compulsive behavior. CBD induced a significant reduction in the number of buried marbles at different doses (15, 30, and 60 mg/kg) compared to controls in a dose-dependent pattern. The same was found with the administration of the ISRS paroxetine (10 mg/kg) and diazepam (2.5 mg/kg). However, the effects of CBD 30 mg/kg persisted even after seven days of repeated daily administration, whereas the effects of diazepam disappeared. Pre-treatment with WAY (3 mg/kg) counteracted the effects of paroxetine, but did not affect the action of CBD, which was prevented by pre-treatment with the CB1 receptor antagonist AM251 (1 mg/kg).[26] This action of CBD in the MBT was recently replicated by another group using a higher dose (120 mg/kg).[27]

The participation of specific cannabinoid receptors (CB1) in the anxiolytic action of CBD has also been investigated using animal models. In the study with the EPM that reported the antagonism of the anxiolytic effect of intra-dlPAG CBD by WAY, the CB1 receptor antagonist AM251 was unable to avoid this effect.[15] However, this receptor system seems to be involved in another anxiolytic-like action of CBD, according to tests using a procedure known as contextual fear conditioning. In this procedure, animals are pre-conditioned to a hostile environment (foot shocks) and later exposed to the same environment, when they normally present freezing, the duration of which can be monitored as a measure of anxiety. Both CBD and diazepam are successful in attenuating freezing in rats, as well as the increased heart rate and blood pressure induced by re-exposure to the contextually feared environment.[10] This effect of CBD on contextual memory is also produced by the endocannabinoid reuptake inhibitor AM404, which increases the availability of cannabinoids in the synaptic cleft.[28] In this study, the two drugs were injected into the ventricles and their effects were counteracted by the CB1 receptor antagonist SR141716A, suggesting the involvement of the endocannabinoid system in the anxiolytic action of CBD in this model. The pre-limbic region of the prefrontal cortex appears to underlie this effect of CBD, as the reduction in contextual fear produced by systemic administration of CBD (10 mg/kg) is associated with reduced c-Fos expression in this area. In addition, the microinjection of CBD (30 nmol) in the pre-limbic region of the frontal cortex reduced freezing induced by re-exposure to the aversive context.[29] The effects of CBD on contextual fear indicate a possible therapeutic action of this cannabinoid in post-traumatic stress disorder.

Another area that is apparently involved in the anxiolytic-like effects of CBD is the bed nucleus of the stria terminalis (BNST). The intra-BNST injection of CBD (15, 30, and 60 nmol) increased the number of punished licks in Vogel's conflict test and the number of open arm entries in the EPM. These effects were blocked in rats pre-treated with WAY.[30]

CBD was also effective in an ethologic model that investigates behaviors induced by innate fear, the predator-prey paradigm.[31] This procedure was performed using a semi-transparent plexiglass box in the shape of a quadrangular arena (154x72x64 cm) with walls covered with a light-reflecting film and floor in transparent plexiglass over a board of stainless steel divided in 20 equal rectangles. One of the corners of the arena has a shelter box with black walls and a complex maze inside. Three days prior to the experiment, the mice were placed and kept in this arena, with free access to food and water until the day of the trial. The "no threat" group had its behaviors recorded for five minutes. Animals exposed to the predator (snake) were divided into four groups (n = 12/11 per group) and pre-treated with intraperitoneal injections of CBD (0.3, 3 and 30 mg/kg) or vehicle (control group). The group of animals that were not confronted with the predator presented no defensive behaviors. Animals pre-treated with CBD had significant reductions in explosive flight and defensive immobility, responses related to panic models. Risk assessment and defensive attention were unaltered in animals treated with CBD. These results suggest that CBD can be effective in the control of panic attacks.

Human studies

The first evidence of CBD's anxiolytic effects in humans, documented with assessment scales, was published in 1982 in a study on the interaction between CBD and THC.[7] The study sample consisted of eight volunteers with a mean age of 27 years, no health problems and who had not used *Cannabis sativa* in the previous 15 days. In a double-blind procedure, the volunteers received CBD, THC, THC + CBD, diazepam, and placebo in different sequences and days. The results showed that the increased anxiety following the administration of THC was significantly attenuated with the simultaneous administration of CBD (THC + CBD).

Based on this preliminary evidence, researchers decided to investigate a possible anxiolytic action of CBD in experimentally induced anxiety in healthy volunteers using the simulated public speaking (SPS) model.[32] The procedure consists of asking a subject to speak in front of a video camera for a few minutes, while subjective anxiety is measured with self-rated scales and physiological correlates of anxiety are recorded (heart rate, blood pressure, skin conductance). CBD (300 mg), as well as the anxiolytic drugs diazepam (10 mg) and ipsapirone (5 mg), administered in a double-blind design, significantly attenuated SPS-induced anxiety.

The SPS test may be regarded as a good model of anxiety and has apparent validity for social anxiety disorder (SAD), as the fear of speaking in public is considered a central feature in this condition. Therefore, the anxiolytic effect of CBD in healthy volunteers observed in this test led to the hypothesis that this cannabinoid could be effective to treat SAD. This hypothesis was recently tested in 24 patients with SAD who had their performance in the SPS test compared to that of a group of 12 healthy controls.[33] The patients with SAD were divided into two groups of 12, one of which received CBD 600 mg and the other placebo, in a double-blind procedure. The results showed that the levels of anxiety, somatic symptoms, and negative self-assessment were higher in patients who took placebo than in those of the CBD group who performed similarly to healthy controls in some measures.

In another study that investigated the effects of CBD on regional cerebral blood flow (rCBF) in healthy volunteers using single photon emission computed tomography (SPECT), SPS-induced anxiety was reduced in patients receiving CBD.[34] In that study, patients received either CBD (400 mg) or placebo, in a crossed double-blind design, in two experimental sessions with an interval of one week. CBD significantly reduced subjective anxiety as measured by rating scales, while brain activity was increased in the left parahippocampal gyrus and decreased in the left amygdala-hippocampus complex, including the fusiform gyrus. This pattern of SPECT results is compatible with an anxiolytic action.

SPECT was also used later to investigate the neural correlates of CBD's anxiolytic effects in a sample of patients with SAD.[17] A single dose of CBD 400 mg was able to reduce subjective anxiety measures and SPECT showed changes in the same regions previously identified in healthy volunteers.

Functional magnetic resonance imaging (fMRI), which allows the acquisition of larger series of images with better temporal and spatial resolution, was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy volunteers.[35] This experiment showed that CBD (600 mg) attenuated fMRI responses during the recognition of fearful facial expressions in the amygdala and the anterior cingulate, and that this attenuation pattern correlated with skin conductance responses to the stimuli. The same group also reported that the anxiolytic action of CBD occurs by altering the subcortical prefrontal connectivity via amygdala and anterior cingulated.[16]

Conclusion

Together, the results from laboratory animals, healthy volunteers, and patients with anxiety disorders support the proposition of CBD as a new drug with anxiolytic properties. Because it has no psychoactive effects and does not affect cognition; has an adequate safety profile, good tolerability, positive results in trials with humans, and a broad spectrum of pharmacological actions,[36] CBD appears to be the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice.[37] Future studies should test this possibility in clinical trials involving patients with different anxiety disorders, especially panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorder. In addition, because the actions of CBD are biphasic, the adequate therapeutic window for each anxiety disorder remains to be determined.

Regarding the mechanism underlying the anxiolytic effects of CBD, the most consistent evidence points to the involvement of the serotonergic system, probably through direct action on 5-HT1A receptors, although other systems, as the endocannabinoid system itself, may also be implicated. Further investigation is warranted to clarify these issues, especially if we consider that CBD is a drug with a variety of effects in the nervous system.[38-40]

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ARTIGO

Canabidiol, um componente da *Cannabis sativa*, como um ansiolítico

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DESCRITORES:
Canabidiol;
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Transtornos de ansiedade.

Resumo
Objetivos: Revisar e descrever os estudos do constituinte não psicotomimético da *Cannabis sativa*, o canabidiol (CBD), como ansiolítico e discutir seus possíveis mecanismos de ação. *Método*: Os artigos selecionados para a presente revisão foram identificados por meio de busca eletrônica em inglês, português e espanhol nos bancos de dados ISI Web of Knowledge, SciELO, PubMed e PsycINFO e combinando os termos "canabidiol e ansiolíticos", "canabidiol e semelhante ao ansiolítico" e "canabidiol e ansiedade". Foram também revisadas as listas de referências dos artigos incluídos, de revisões da literatura e de capítulos de livro. Incluímos trabalhos experimentais em humanos e em animais, sem limite de tempo. *Resultados*: Estudos com modelos animais de ansiedade e envolvendo voluntários saudáveis sugerem claramente que o CBD possui efeitos ansiolíticos. Além disso, o CBD mostrou-se capaz de reduzir a ansiedade em pacientes com transtorno de ansiedade social. *Conclusão*: Futuros ensaios clínicos com pacientes portadores de diferentes transtornos de ansiedade, em especial pacientes com transtorno do pânico, obsessivo-compulsivo, ansiedade social e estresse pós-traumático, são oportunos. Além disso, ainda é necessário determinar a adequada faixa terapêutica do CBD e os exatos mecanismos envolvidos nessa ação ansiolítica.

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Introdução

Cannabis sativa é a droga de abuso mais utilizada em todo o mundo, e cerca de 20% da população mundial de jovens a usam de forma abusiva e regular.[1] O principal componente psicoativo da planta é o delta-9-tetrahidrocanabinol (Δ9-THC), uma das substâncias responsáveis pelos efeitos psicoativos da maconha.[2-4]

O canabidiol (CBD) é outro composto abundante na *Cannabis sativa*, constituindo cerca de 40% das substâncias ativas da planta.[5] Os efeitos farmacológicos do CBD são diferentes e muitas vezes opostos aos do Δ9-THC.[6] O número de publicações sobre o CDB aumentou consideravelmente nos últimos anos e sustenta a ideia de que o CBD possui uma gama de possíveis efeitos terapêuticos; entre essas possibilidades, as propriedades ansiolíticas e antipsicóticas se destacam.[7-10] Os efeitos ansiolíticos do CBD são, aparentemente, semelhantes àqueles dos medicamentos aprovados para tratar a ansiedade,[11] embora suas doses efetivas não tenham sido claramente estabelecidas e os mecanismos subjacentes a esses efeitos não sejam totalmente compreendidos. A baixa afinidade do CBD para neurorreceptores canabinoides[12,13] e suas propriedades agonistas nos receptores 5-HT1A[14,15] foram demonstradas repetidamente.

A maioria dos estudos sobre o CDB foi realizada em roedores, mas estudos usando amostras de seres humanos também forneceram resultados promissores.[16,17] Portanto, o objetivo deste trabalho foi revisar a literatura científica sobre as propriedades ansiolíticas do CBD em animais e em seres humanos.

Método

Os artigos selecionados para esta revisão foram identificados por meio de buscas em inglês, português e espanhol em bancos de dados eletrônicos ISI Web of Knowledge, SciELO, PubMed e PsycINFO e combinando os termos de busca "canabidiol e ansiolítico", "canabidiol e semelhante ao ansiolítico" e "canabidiol e ansiedade". Além disso, as listas de referências dos artigos selecionados, revisões da literatura e capítulos de livros relevantes foram pesquisadas manualmente em busca de referências adicionais. Estudos experimentais com amostras humanas e animais foram incluídos e não houve limite de tempo. Buscamos excluir os estudos que avaliaram o fumo de *Cannabis*, pois não é possível estabelecer a dose, a composição e a proporção dos diferentes canabinoides nesse caso, além das grandes variações individuais nas amostras inscritas. Por fim, não incluímos estudos utilizando extratos contendo tanto THC como CBD na forma oral (Cannador®) ou de spray bucal (Sativex®) devido à dificuldade de estabelecer os efeitos somente do CBD (Tabela 1).

Estudos de Animais

Os dois primeiros artigos sobre os efeitos do CBD na ansiedade experimental foram publicados em revistas que não estavam indexadas nos bancos de dados utilizados para esta revisão, mas foram localizados através da busca manual nas listas de referências da literatura relevante. Esses dois trabalhos mostraram resultados contraditórios. Em um deles, não foram observados efeitos significativos de altas doses de CBD (100 mg/kg) em ratos no teste de conflito de Geller Seifter.[18] No outro, uma dose baixa de CDB (10 mg/kg) causou efeitos ansiolíticos em ratos submetidos ao teste de resposta emocional condicionada.[19]

Estudos posteriores utilizando o labirinto em cruz elevado (LCE) ajudaram a elucidar essa contradição.[9] O LCE consiste em dois braços abertos opostos (50 x 10 cm) e dois braços fechados (50 x 10 x 40 cm) que se cruzam em sua porção central. Os braços são feitos de madeira e ficam a 50 cm do solo. Nesse estudo, os ratos injetados com CDB, diazepam ou veículo (substâncias inativas) foram colocados no centro do labirinto de frente para os braços fechados. Os tempos gastos e os números de entradas nos braços abertos e fechados foram medidos durante 10 minutos. A frequência de entradas nos braços abertos dos animais que receberam CBD apresentou uma curva em forma de U invertido, com taxas significativamente mais elevadas do que as observadas em animais tratados com veículo, nas doses de 2,5, 5 e 10 mg/kg. As medidas dos ratos tratados com 20 mg/kg de CDB não diferiram daquelas dos controles, sugerindo que os efeitos ansiolíticos somente estão presentes em baixas doses, o que explica a ausência dos efeitos relatados com 100 mg/kg de CDB em 1981.[18] A mesma curva em forma de U invertido da resposta à dose foi obtida com uma grande variedade de doses de CBD no LCE (Onaivi *et al*.).[20] Além disso, o mesmo padrão foi observado com a infusão direta de CBD na substância cinzenta periaquedutal (SCP) de ratos testados no LCE,[15,21] confirmando que os efeitos ansiolíticos somente devem ser esperados ao uso de doses baixas de CBD.

Os mecanismos pelos quais o CBD atua para diminuir a ansiedade foram estudados em vários modelos animais de ansiedade usando roedores. Um desses estudos usou o teste de conflito de Vogel,[22] no qual o animal é privado de água e colocado em uma gaiola com a parte inferior da grade eletrificada através da qual o animal recebe um choque após lamber a água por um número pré-determinado de vezes. Três substâncias foram testadas em ratos, utilizando o seguinte procedimento: CBD (2,5, 5 e 10 mg/kg), diazepam e flumazenil (um antagonista dos receptores de benzodiazepina), além de veículo (placebo). Os testes mostraram que o CBD produziu efeitos consistentes com os do diazepam, aumentando o número de lambidas mesmo que resultassem em punição. Flumazenil antagonizou o efeito ansiolítico do diazepam, mas não o do CBD, sugerindo que os efeitos do CBD não são mediados pela ativação dos receptores de benzodiazepina.

Há evidências fortes mostrando que o sistema serotoninérgico está envolvido na ação ansiolítica do CBD. A injeção do antagonista do receptor 5-HT1A, o WAY-100635 (WAY), diretamente na SCP dorsolateral (SCPdl) de ratos antagonizou os efeitos ansiolíticos do CBD no LCE e no teste de conflito de Vogel.[15] A participação dos receptores 5-HT1A na ação ansiolítica do CBD também foi derivada das respostas comportamentais e cardiovasculares ao estresse em ratos.[11] Nesse estudo, os animais foram intraperitonealmente injetados com veículo ou CBD (1, 10 e 20 mg/kg) e, após 30 minutos, foram confinados durante 60 minutos. A imobilização aumentou a pressão arterial, a frequência cardíaca e as respostas de ansiedade no LCE 24 horas depois, e esses efeitos foram atenuados pelo CBD. O pré-tratamento com WAY-100635 bloqueou a ação ansiolítica do CBD. A injeção de CDB intra-SCP dorsal também bloqueou as respostas semelhantes ao pânico no labirinto em T elevado (LTE) e

Tabela 1 Estudos em humanos e animais sobre o efeito ansiolítico de canabidiol

Estudo	Modelo	Via	Dose	Efeito ansiolítico
Animais				
Silveira Filho *et al*.[18]	Teste de conflito	Intraperitoneal	100 mg/kg	–
Zuardi *et al*.[19]	Paradigma de resposta emocional condicionada	Intraperitoneal	10 mg/kg	+
Onaivi *et al*.[20]	Teste de labirinto em cruz elevado	Intraperitoneal	0,01, 0,1, 0,5, 1,0, 2,5, 5,0, 10,0, 50,0 e 100,0 mg/kg	+
Guimarães *et al*.[9]	Teste de labirinto em cruz elevado	Intraperitoneal	2,5, 5,0, 10,0 e 20,0 mg/kg	+
Moreira *et al*.[22]	Teste de conflito de Vogel	Intraperitoneal	2,5, 5,0 e 10,0 mg/kg	+
Resstel *et al*.[10]	Condicionamento contextual de medo	Intraperitoneal	10 mg/kg	+
Campos *et al*.[15]	Teste de labirinto em cruz elevado e teste de conflito de Vogel	Intrassubstância cinzenta periaquedutal dorsal		+
Bitencourt *et al*.[28]	Condicionamento contextual de medo	i.c.v.	2,0 microg/microl	+
Campos *et al*.[21]	Teste de labirinto em cruz elevado	Intrassubstância cinzenta periaquedutal dorsal	30 ou 60 nmol	+
Resstel *et al*.[19]	Estresse por confinamento	Intraperitoneal	1, 10 e 20 mg/kg	+
Soares *et al*.[23]	Labirinto em T elevado	Intrassubstância cinzenta periaquedutal dorsal	15, 30 ou 60 nmol	+
Lemos *et al*.[29]	Condicionamento contextual de medo	Intraperitoneal e microinjeção direta no córtex pré-frontal PL	10 mg/kg (i.p) e 30 nmol (microinjeção no córtex pré-frontal PL)	+
Casarotto *et al*.[26]	Teste de enterrar bolas de gude	Intraperitoneal	15, 30 e 60 mg/kg	+
Gomes *et al*.[30]	Teste de conflito de Vogel	Intranúcleo do leito da estria terminal	15, 30, e 60 nmol	+
Deiana *et al*.[27]	Teste de enterrar bolas de gude	Intraperitoneal e oral	120 mg/kg	+
Uribe-Mariño *et al*.[31]	Paradigma predador-presa	Intraperitoneal	0,3, 3,0 and 30 mg/kg	+
Campos *et al*.[24]	Labirinto em T elevado	Oral		+
Seres Humanos				
Zuardi *et al*.[7]	Redução dos escores elevados no IDATE induzida por THC (voluntários saudáveis)	Oral	1 mg/kg	+
Zuardi *et al*.[32]	Redução dos escores dos fatores de ansiedade na VAS após falar em público (voluntários saudáveis)	Oral	300 mg	+
Crippa *et al*.[34]	Redução dos escores dos fatores de ansiedade na VAS antes do procedimento SPECT (voluntários saudáveis)	Oral	400 mg	+
Fusar-Poli *et al*.[35]	Redução na flutuação da condutância da pele na tarefa de expressões faciais de medo em RMf (voluntários saudáveis)	Oral	600 mg	+
Crippa *et al*.[17]	Redução dos escores dos fatores de ansiedade na VAS antes do procedimento SPECT (pacientes com fobia social)	Oral	400 mg	+
Bergamaschi *et al*.[33]	Redução dos escores dos fatores de ansiedade na VAS após falar em público (pacientes com fobia social)	Oral	600 mg	+

as respostas de fuga à estimulação elétrica dessa área.[23] O LTE tem três braços com as mesmas dimensões, dois abertos e um fechado, e permite medir a evitação de entrada nos braços abertos quando o animal é colocado no braço fechado, bem como de fuga quando o animal é colocado no braço aberto. A resposta semelhante à de pânico observada com o CBD nos dois procedimentos foi antagonizada pela administração prévia intra-SCPdl do WAY.[22] A administração oral crônica de CBD também teve efeitos antipânico no LTE, que foram neutralizados pela administração intra-SCPdl do WAY. No entanto, a administração crônica de CBD não alterou a concentração extracelular de serotonina na SCPdl ou a expressão dos receptores 5-HT1A ou 5-HT2C, indicando que o CBD ativa diretamente os receptores 5-HT1A.[24] Descobriu-se que o CBD também ativa o receptor vaniloide tipo 1 (TRPV1)[25] e há evidências de que essa ativação pode explicar a forma da curva em U invertido da resposta de efeito ansiolítico do CBD observada no LCE. Os receptores TRPV1 regulam a libertação de glutamato na SCPdl e o aumento da ativação desse sistema resultaria no aumento da ansiedade. Portanto, foi sugerido que doses elevadas de CBD na SCPdl podem ativar os receptores TRPV1 locais, facilitando a neurotransmissão glutamatérgica e aumentando a ansiedade.

Para testar essa hipótese, os ratos pré-tratados com o antagonista TRPV1 capsazepina na SCPdl receberam injeções de CBD (30 e 60 mg/kg) na mesma região e foram testados no LCE. A dose de 60 mg/kg de CBD, que não havia apresentado ação ansiolítica anteriormente, foi capaz de reduzir a ansiedade após pré-tratamento com capsazepina, sugerindo que a ativação dos receptores TRPV1 pela dose mais elevada de CBD contrabalançaria o efeito ansiolítico do CBD produzido pela ativação dos receptores 5-HT1A.[21]

Como a serotonina também está envolvida no transtorno obsessivo-compulsivo (TOC), os efeitos do CBD foram testados em ratos submetidos ao teste de enterrar bolas de gude (TEBG), um modelo animal de comportamento compulsivo. O CBD induziu uma redução significativa no número de bolas enterradas em doses diferentes (15, 30 e 60 mg/kg), na comparação com controles em um padrão dose-dependente. O mesmo foi observado com a administração de ISRS paroxetina (10 mg/kg) e diazepam (2,5 mg/kg). No entanto, os efeitos do CBD na dose de 30 mg/kg persistiram, mesmo após sete dias de administração repetida diária, enquanto os efeitos do diazepam desapareceram. O pré-tratamento com WAY (3 mg/kg) neutralizou os efeitos da paroxetina, mas não afetou a ação do CBD, a qual foi evitada pelo pré-tratamento com o antagonista do receptor CB1, AM251, (1 mg/kg).[26] Essa ação do CBD no TEBG foi recentemente replicada por um outro grupo usando uma dose mais elevada (120 mg/kg).[27]

A participação dos receptores canabinoides específicos (CB1) na ação ansiolítica do CBD também foi investigada com o uso de modelos animais. No estudo com o LCE que relatou o antagonismo do efeito ansiolítico do CBD intra-SCPdl causado pelo WAY, o antagonista do receptor CB1, AM251, foi incapaz de evitar esse efeito.[15] No entanto, o sistema desse receptor parece estar envolvido em outra ação ansiolítica semelhante à do CBD, de acordo com testes utilizando um procedimento conhecido como condicionamento contextual de medo. Nesse procedimento, os animais são pré-condicionados a um ambiente hostil (choques nos pés) e posteriormente expostos ao mesmo ambiente, quando eles normalmente apresentam resposta de congelamento, cuja duração pode ser monitorizada como uma medida da ansiedade. Tanto o CBD quanto o diazepam são efetivos para atenuar a resposta de congelamento em ratos, bem como o aumento da frequência cardíaca e da pressão sanguínea induzido pela reexposição ao ambiente contextualmente temido.[10] Esse efeito do CBD sobre a memória contextual também é produzido pelo inibidor da recaptação de endocanabinoides, AM404, o qual aumenta a disponibilidade de canabinoides na fenda sináptica.[28] Nesse estudo, as duas drogas foram injetadas nos ventrículos e seus efeitos foram neutralizados pelo antagonista dos receptores CB1, SR141716A, sugerindo o envolvimento do sistema endocanabinoide na ação ansiolítica do CBD nesse modelo. A região pré-límbica do córtex pré-frontal parece ser a base desse efeito do CBD, pois a redução do medo contextual produzida pela administração sistêmica do CBD (10 mg/kg) está associada à redução da expressão de c-Fos nessa área. Além disso, a microinjeção de CBD (30 nmol) na região pré-límbica do córtex frontal reduziu a resposta de congelamento induzida pela reexposição ao contexto aversivo.[29] Os efeitos do CBD sobre o medo contextual indicam uma possível ação terapêutica desse canabinoide no transtorno do estresse pós-traumático.

Outra área que aparentemente está envolvida nos efeitos ansiolíticos semelhantes aos do CBD é o núcleo leito da estria terminal (NLET). A injeção intra-NLET de CBD (15, 30 e 60 nmol) aumentou o número de lambidas punidas no teste de conflito de Vogel e o número de entradas nos braços abertos do LCE. Esses efeitos foram bloqueados em ratos pré-tratados com WAY.[30]

O CBD também foi eficaz em um modelo etológico que investiga os comportamentos induzidos pelo medo inato, o paradigma predador-presa.[31] Esse procedimento foi realizado usando uma caixa semitransparente de plexiglas na forma de uma arena quadrangular (154 x 72 x 64 cm) com as paredes cobertas com uma película refletora de luz e piso em plexiglas transparente sobre uma placa de aço inoxidável dividida em 20 retângulos iguais. Um dos cantos da arena tem uma caixa de abrigo com paredes pretas e um labirinto complexo no interior. Três dias antes do experimento, os ratos foram colocados e mantidos nessa arena, com livre acesso à comida e água até o dia do ensaio. O comportamento do grupo "não ameaçado" foi registrado durante cinco minutos. Os animais expostos ao predador (cobra) foram divididos em quatro grupos (n = 12/11 por grupo) e pré-tratados com injeções intraperitoneais de CBD (0,3, 3 e 30 mg/kg) ou veículo (grupo controle). O grupo dos animais que não foram confrontados com o predador não apresentou comportamento defensivo. Os animais pré-tratados com CBD apresentaram reduções significativas em fuga explosiva e imobilidade defensiva, respostas relacionadas aos modelos de pânico. As avaliações de risco e atenção defensiva não mostraram alteração nos animais tratados com CBD. Esses resultados sugerem que o CBD pode ser efetivo no controle dos ataques de pânico.

Estudos em Humanos

A primeira evidência dos efeitos ansiolíticos do CBD em humanos, documentada com escalas de avaliação, foi publicada em 1982 em um estudo sobre a interação entre CBD e THC.[7] A amostra do estudo foi composta por oito voluntários com idade média de 27 anos, sem problemas de

saúde e que não haviam usado *Cannabis sativa* nos últimos 15 dias. Em um procedimento duplo-cego, os voluntários receberam CBD, THC, THC + CBD, diazepam e placebo em diferentes sequências e dias. Os resultados mostraram que o aumento da ansiedade após a administração de THC foi significativamente atenuado à administração simultânea de CDB (THC + CBD).

Com base nessas evidências preliminares, os pesquisadores decidiram investigar uma possível ação ansiolítica do CBD na ansiedade induzida experimentalmente em voluntários saudáveis usando o modelo de simulação de falar em público (SFP).[32] O procedimento consiste em pedir ao sujeito para falar em frente a uma câmera de vídeo por alguns minutos, enquanto a ansiedade subjetiva é medida com escalas de autoavaliação e os correlatos fisiológicos de ansiedade são registrados (frequência cardíaca, pressão arterial, condutância da pele). O CBD (300 mg), bem como as drogas ansiolíticas diazepam (10 mg) e ipsapirona (5 mg), administrado de modo duplo-cego, atenuou significativamente a ansiedade induzida pela SFP.

O teste de SFP pode ser considerado um bom modelo de ansiedade e tem validade aparente para o transtorno de ansiedade social (TAS), pois o medo de falar em público é considerado uma característica central nessa condição. Portanto, o efeito ansiolítico do CBD em voluntários saudáveis observado nesse teste levou à hipótese de que esse canabinoide poderia ser eficaz para tratar o TAS. Essa hipótese foi recentemente testada em 24 pacientes com TAS que tiveram seus desempenhos no teste de SFP comparados àqueles de um grupo de 12 controles saudáveis.[33] Os pacientes com TAS foram divididos em dois grupos de 12, um dos quais recebeu 600 mg de CBD e o outro, placebo, em procedimento duplo-cego. Os resultados mostraram que os níveis de ansiedade, sintomas somáticos e autoavaliação negativa nos pacientes que receberam placebo foram maiores do que naqueles do grupo CBD que tiveram desempenhos semelhantes aos controles saudáveis em algumas medidas.

Em outro estudo que investigou os efeitos do CBD sobre o fluxo sanguíneo cerebral regional (FSCr) em voluntários saudáveis, usando tomografia computadorizada por emissão de fóton único (SPECT), a ansiedade induzida pela SFP foi reduzida nos pacientes que receberam CBD.[34] Nesse estudo, os pacientes receberam CBD (400 mg) ou placebo, em uma abordagem duplo-cega cruzada, em duas sessões experimentais com um intervalo de uma semana. O CBD reduziu significativamente a ansiedade subjetiva medida por escalas de avaliação, enquanto a atividade cerebral foi aumentada no giro hipocampal esquerdo e diminuída no complexo amígdala-hipocampo esquerdo, incluindo o giro fusiforme. Esse padrão de resultados na SPECT é compatível com uma ação ansiolítica.

A SPECT também foi usada posteriormente para investigar os correlatos neurais dos efeitos ansiolíticos do CBD em uma amostra de pacientes com TAS.[17] Uma única dose de CBD (400 mg) conseguiu reduzir as medidas de ansiedade subjetiva e a SPECT mostrou alterações nas mesmas regiões previamente identificadas nos voluntários saudáveis.

A ressonância magnética funcional (RMf), que permite a aquisição de uma série maior de imagens com melhor resolução temporal e espacial, foi usada para investigar os correlatos neurais dos efeitos ansiolíticos do CBD em 15 voluntários saudáveis.[35] Esse experimento mostrou que o CBD (600 mg) atenuou as respostas observadas na RMf durante o reconhecimento das expressões faciais de medo na amígdala e no cíngulo anterior, e que esse padrão de atenuação correlacionou com as respostas da condutância da pele aos estímulos. O mesmo grupo também relatou que a ação ansiolítica do CBD ocorre pela alteração da conectividade subcortical pré-frontal via amígdala e cíngulo anterior.[16]

Conclusão

Em conjunto, os resultados de estudos em animais de laboratório, voluntários saudáveis e pacientes com transtornos de ansiedade sustentam a proposta do CBD como uma nova droga com propriedades ansiolíticas. Como o CBD não tem efeitos psicoativos e não afeta a cognição, possui um perfil de segurança adequado, boa tolerabilidade, resultados positivos em testes com seres humanos e um amplo espectro de ações farmacológicas,[36] esse composto canabinoide parece estar mais próximo de ter suas descobertas preliminares na ansiedade traduzidas para a prática clínica.[37] Estudos futuros devem testar essa possibilidade em ensaios clínicos envolvendo pacientes com diferentes transtornos de ansiedade, especialmente os transtornos do pânico, obsessivo-compulsivo, de ansiedade social e pós-traumático. Além disso, como as ações do CBD são bifásicas, a janela terapêutica adequada para cada distúrbio de ansiedade ainda precisa ser determinada. Com relação ao mecanismo subjacente aos efeitos ansiolíticos do CBD, as evidências mais consistentes apontam para o envolvimento do sistema serotoninérgico, provavelmente através da ação direta dos receptores 5-HT1A, embora outros sistemas, como o próprio sistema endocanabinoide, também podem estar envolvidos. Estudos complementares são necessários para esclarecer essas questões, especialmente se considerarmos que o CBD é uma droga com uma variedade de efeitos no sistema nervoso.[38-40]

Declarações

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** Modesto*

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REVIEW

Cannabidiol as a Potential Treatment for Anxiety Disorders

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Abstract Cannabidiol (CBD), a *Cannabis sativa* constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

Keywords Cannabidiol · Endocannabinoids · Anxiety · Generalized anxiety disorder · Post-traumatic stress disorder

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Introduction

Fear and anxiety are adaptive responses essential to coping with threats to survival. Yet excessive or persistent fear may be maladaptive, leading to disability. Symptoms arising from excessive fear and anxiety occur in a number of neuropsychiatric disorders, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and obsessive–compulsive disorder (OCD). Notably, PTSD and OCD are no longer classified as anxiety disorders in the recent revision of the Diagnostic and Statistical Manual of Mental Disorders-5; however, excessive anxiety is central to the symptomatology of both disorders. These anxiety-related disorders are associated with a diminished sense of well-being, elevated rates of unemployment and relationship breakdown, and elevated suicide risk [1–3]. Together, they have a lifetime prevalence in the USA of 29 % [4], the highest of any mental disorder, and constitute an immense social and economic burden [5, 6].

Currently available pharmacological treatments include serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressant drugs, and partial 5-hydroxytryptamine (5-HT)$_{1A}$ receptor agonists. Anticonvulsants and atypical antipsychotics are also used to treat PTSD. These medications are associated with limited response rates and residual symptoms, particularly in PTSD, and adverse effects may also limit tolerability and adherence [7–10]. The substantial burden of anxiety-related disorders and the limitations of current treatments place a high priority on developing novel pharmaceutical treatments.

Cannabidiol (CBD) is a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of Δ^{9}-tetrahydrocannabinol (THC). CBD has broad therapeutic properties across a range of neuropsychiatric disorders, stemming from diverse central nervous system actions [11, 12]. In recent

years, CBD has attracted increasing interest as a potential anxiolytic treatment [13–15]. The purpose of this review is to assess evidence from current preclinical, clinical, and epidemiological studies pertaining to the potential risks and benefits of CBD as a treatment for anxiety disorders.

Methods

A search of MEDLINE (PubMed), PsycINFO, Web of Science Scopus, and the Cochrane Library databases was conducted for English-language papers published up to 1 January 2015, using the search terms "cannabidiol" and "anxiety" or "fear" or "stress" or "anxiety disorder" or "generalized anxiety disorder" or "social anxiety disorder" or "social phobia" or "post-traumatic stress disorder" or "panic disorder" or "obsessive compulsive disorder". In total, 49 primary preclinical, clinical, or epidemiological studies were included. Neuroimaging studies that documented results from anxiety-related tasks, or resting neural activity, were included. Epidemiological or clinical studies that assessed CBD's effects on anxiety symptoms, or the potential protective effects of CBD on anxiety symptoms induced by cannabis use (where the CBD content of cannabis is inferred via a higher CBD:THC ratio), were included.

CBD Pharmacology Relevant to Anxiety

General Pharmacology and Therapeutic Profile

Cannabis sativa, a species of the *Cannabis* genus of flowering plants, is one of the most frequently used illicit recreational substances in Western culture. The 2 major phyto- cannabinoid constituents with central nervous system activity are THC, responsible for the euphoric and mind-altering effects, and CBD, which lacks these psychoactive effects. Preclinical and clinical studies show CBD possesses a wide range of therapeutic properties, including antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties (see [11, 12, 16–19] for reviews). A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities noted [20].

CBD has a broad pharmacological profile, including interactions with several receptors known to regulate fear and anxiety-related behaviors, specifically the cannabinoid type 1 receptor (CB_1R), the serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor [11, 12, 19, 21]. In addition, CBD may also regulate, directly or indirectly, the peroxisome proliferator-activated receptor-γ, the orphan G-protein-coupled receptor 55, the equilibrative nucleoside transporter, the adenosine transporter, additional TRP channels, and glycine receptors [11, 12, 19, 21]. In the current review of primary studies, the following receptor-specific actions were found to have been investigated as potential mediators of CBD's anxiolytic action: CB_1R, TRPV1 receptors, and 5-HT_{1A} receptors. Pharmacology relevant to these actions is detailed below.

The Endocannabinoid System

Following cloning of the endogenous receptor for THC, namely the CB_1R, endogenous CB_1R ligands, or "endocannabinoids" (eCBs) were discovered, namely anandamide (AEA) and 2-arachidonoylglycerol (reviewed in [22]). The CB_1R is an inhibitory $G_{i/o}$ protein-coupled receptor that is mainly localized to nerve terminals, and is expressed on both γ-aminobutryic acid-ergic and glutamatergic neurons. eCBs are fatty acid derivatives that are synthesized on demand in response to neuronal depolarization and Ca^{2+} influx, via cleavage of membrane phospholipids. The primary mechanism by which eCBs regulate synaptic function is retrograde signaling, wherein eCBs produced by depolarization of the postsynaptic neuron activate presynaptic CB_1Rs, leading to inhibition of neurotransmitter release [23]. The "eCB system" includes AEA and 2-arachidonoylglycerol; their respective degradative enzymes fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase; the CB_1R and related CB_2 receptor (the latter expressed mainly in the periphery); as well as several other receptors activated by eCBs, including the TRPV1 receptor, peroxisome proliferator-activated receptor-γ, and G protein-coupled 55 receptor, which functionally interact with CB_1R signaling (reviewed in [21, 24]). Interactions with the TRPV1 receptor, in particular, appear to be critical in regulating the extent to which eCB release leads to inhibition or facilitation of presynaptic neurotransmitter release [25]. The TRPV1 receptor is a postsynaptic cation channel that underlies sensation of noxious heat in the periphery, with capsacin (hot chili) as an exogenous ligand. TRPV1 receptors are also expressed in the brain, including the amygdala, periaqueductal grey, hippocampus, and other areas [26, 27].

The eCB system regulates diverse physiological functions, including caloric energy balance and immune function [28]. The eCB system is also integral to regulation of emotional behavior, being essential to forms of synaptic plasticity that determine learning and response to emotionally salient, particularly highly aversive events [29, 30]. Activation of CB_1Rs produces anxiolytic effects in various models of unconditioned fear, relevant to multiple anxiety disorder symptom domains (reviewed in [30–33]). Regarding conditioned fear, the effect of CB_1R activation is complex: CB_1R activation may enhance or reduce fear expression, depending on brain locus and the eCB ligand [34]; however, CB_1R activation potently enhances fear extinction [35], and can prevent fear reconsolidation. Genetic manipulations that impede

CB_1R activation are anxiogenic [35], and individuals with eCB system gene polymorphisms that reduce eCB tone—for example, FAAH gene polymorphisms—exhibit physiological, psychological, and neuroimaging features consistent with impaired fear regulation [36]. Reduction of AEA–CB_1R signaling in the amygdala mediates the anxiogenic effects of corticotropin-releasing hormone [37], and CB_1R activation is essential to negative feedback of the neuroendocrine stress response, and protects against the adverse effects of chronic stress [38, 39]. Finally, chronic stress impairs eCB signaling in the hippocampus and amygdala, leading to anxiety [40, 41], and people with PTSD show elevated CB_1R availability and reduced peripheral AEA, suggestive of reduced eCB tone [42].

Accordingly, CB_1R activation has been suggested as a target for anxiolytic drug development [15, 43, 44]. Proposed agents for enhancing CB_1R activation include THC, which is a potent and direct agonist; synthetic CB_1R agonists; FAAH inhibitors and other agents that increase eCB availability, as well as nonpsychoactive cannabis phytocannabinoids, including CBD. While CBD has low affinity for the CB_1R, it functions as an indirect agonist, potentially via augmentation of CB_1R constitutional activity, or via increasing AEA through FAAH inhibition (reviewed in [21]).

Several complexities of the eCB system may impact upon the potential of CBD and other CB_1R-activating agents to serve as anxiolytic drugs. First, CB_1R agonists, including THC and AEA, have a biphasic effect: low doses are anxiolytic, but higher doses are ineffective or anxiogenic, in both preclinical models in and humans (reviewed in [33, 45]). This biphasic profile may stem from the capacity of CB_1R agonists to also activate TRPV1 receptors when administered at a high, but not low dose, as demonstrated for AEA [46]. Activation of TRPV1 receptors is predominantly anxiogenic, and thus a critical balance of eCB levels, determining CB1 *versus* TRPV1 activation, is proposed to govern emotional behavior [27, 47]. CBD acts as a TRPV1 agonist at high concentrations, potentially by interfering with AEA inactivation [48]. In addition to dose-dependent activation of TRPV1 channels, the anxiogenic *versus* anxiolytic balance of CB_1R agonists also depends on dynamic factors, including environmental stressors [33, 49].

5-HT_{1A} Receptors

The 5-HT_{1A} receptor (5-$HT_{1A}R$) is an established anxiolytic target. Buspirone and other 5-$HT_{1A}R$ agonists are approved for the treatment of GAD, with fair response rates [50]. In preclinical studies, 5-$HT_{1A}R$ agonists are anxiolytic in animal models of general anxiety [51], prevent the adverse effects of stress [52], and enhance fear extinction [53]. Both pre- and postsynaptic 5-$HT_{1A}Rs$ are coupled to various members of the $G_{i/o}$ protein family. They are expressed on serotonergic neurons in the raphe, where they exert autoinhibitory function, and various other brain areas involved in fear and anxiety [54, 55]. Mechanisms underlying the anxiolytic effects of 5-$HT_{1A}R$ activation are complex, varying between both brain region, and pre- *versus* postsynaptic locus, and are not fully established [56]. While in vitro studies suggest CBD acts as a direct 5-$HT_{1A}R$ agonist [57], in vivo studies are more consistent with CBD acting as an allosteric modulator, or facilitator of 5-HT_{1A} signaling [58].

Preclinical Evaluations

Generalized Anxiety Models

Relevant studies in animal models are summarized in chronological order in Table 1. CBD has been studied in a wide range of animal models of general anxiety, including the elevated plus maze (EPM), the Vogel-conflict test (VCT), and the elevated T maze (ETM). See Table 1 for the anxiolytic effect specific to each paradigm. Initial studies of CBD in these models showed conflicting results: high (100 mg/kg) doses were ineffective, while low (10 mg/kg) doses were anxiolytic [59, 60]. When tested over a wide range of doses in further studies, the anxiolytic effects of CBD presented a bell-shaped dose–response curve, with anxiolytic effects observed at moderate but not higher doses [61, 90]. All further studies of acute systemic CBD without prior stress showed anxiolytic effects or no effect [62, 65], the latter study involving intracerebroventricular rather than the intraperitoneal route. No anxiogenic effects of acute systemic CBD dosing in models of general anxiety have yet been reported. As yet, few studies have examined chronic dosing effects of CBD in models of generalized anxiety. Campos et al. [66] showed that in rat, CBD treatment for 21 days attenuated inhibitory avoidance acquisition [83]. Long et al. [69] showed that, in mouse, CBD produced moderate anxiolytic effects in some paradigms, with no effects in others.

Anxiolytic effects of CBD in models of generalized anxiety have been linked to specific receptor mechanisms and brain regions. The midbrain dorsal periaqueductal gray (DPAG) is integral to anxiety, orchestrating autonomic and behavioral responses to threat [91], and DPAG stimulation in humans produces feelings of intense distress and dread [92]. Microinjection of CBD into the DPAG produced anxiolytic effects in the EPM, VGC, and ETM that were partially mediated by activation of 5-$HT_{1A}Rs$ but not by CB_1Rs [65, 68]. The bed nucleus of the stria terminalis (BNST) serves as a principal output structure of the amygdaloid complex to coordinate sustained fear responses, relevant to anxiety [93]. Anxiolytic effects of CBD in the EPM and VCT occurred upon microinjection into the BNST, where they depended on 5-$HT_{1A}R$

Table 1 Preclinical studies

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Silveira Filho et al. [59]	WR	i.p.	**100** mg/kg, acute	GSCT	No effect	NA
Zuardi et al. [60]	WR	i.p.	**10**mg/kg, acute	CER	Anxiolytic	NA
Onaivi et al. [61]	ICR mice	i.p.	0.01, 0.10, **0.50**, **1.00**, **2.50**, **5.00**, **10.00**, **50.00**, 100.00 mg/kg, acute	EPM	Anxiolytic	Effects ↓ by IP flumazenil, unchanged by naloxone
Guimaraes et al. [61]	WR	i.p.	**2.5**, **5.0**, **10.0** and 20.0 mg/kg, acute	EPM	Anxiolytic	NA
Moreira et al. [62]	WR	i.p.	2.5, 5.0 and **10.0**mg/kg, acute	VCT	Anxiolytic	Effect unchanged by IP flumazenil
Resstel et al. [63]	WR	i.p.	**10**mg/kg, acute	CFC	Anxiolytic	NA
Campos et al. [64]	WR	dlPAG	15.0, **30.0**, 60.0 nmol/0.2 μl, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra-dlPAG WAY100635 but not intra-dlPAG AM251
Bitencourt et al. [65]	WR	i.c.v.	**2.0** μg/μl 5 min before extinction, acute	CFC extinction EPM before and 24 h after CFC	Anxiolytic No effect before CFC Anxiolytic following CFC	Extinction effect ↓ by SR141716A but not capsazepine
Campos et al. [66]	WR	dlPAG	**30**, 60 mg/kg, acute	EPM	Anxiolytic	Intra-dlPAG capsazepine renders 60 mg/kg anxiolytic
Resstel et al. [67]	WR	i.p.	1, **10** or 20 mg/kg, acute	RS EPM 24 h following RS	Anxiolytic, ↓ Pressor ↓ Tachycardia Anxiolytic	All effects ↓ by systemic WAY100635
Soares et al. [68]	WR	dlPAG	15, **30** or **60**nmol, acute	ETM PAG E-stim	Anxiolytic Panicolytic Panicolytic	All effects ↓ by intra-dlPAG WAY100635 but not AM251
Long et al. [69]	C57BL/6 J mice	i.p.	**1**, 5, 10, **50**mg/kg, chronic, daily/21 d	EPM L-DT SI OF	No effect 1 mg/kg anxiolytic No effect 50 mg/kg anxiolytic	NA
Lemos et al. [70]	WR	i.p. PL IL	**10**mg/kg IP, **30**nmol intra-PL and intra-IL, acute	CFC	IP and PL anxiolytic IL anxiogenic	NA
Casarotto et al. [71]	C57BL/6 J mice	i.p.	15, **30**, and 60 mg/kg, acute, or subchronic, daily/7 d	MBT	Anticompulsive	Effect ↓ by IP AM251 but not WAY100635
Gomes et al. [72]	WR	BNST	15, **30**, and 60 nmol, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra BNST WAY100635
Granjeiro et a l. [73]	WR	Intracisternal	15, **30**, and 60 nmol, acute	RS EPM 24 h after RS	Anxiolytic, ↓Pressor ↓Tachycardia Anxiolytic	NA
Deiana et al. [74]	SM	i.p. Oral	**120**mg/kg, acute	MBT	Anticompulsive	NA
Uribe-Marino et al. [75]	SM	i.p.	0.3, **3.0**, **30.0**mg/kg, acute	PS	Panicolytic	NA

Table 1 (continued)

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Stern et al. [76]	WR	i.p.	3, **10**, 30 mg/kg immediately after retrieval, acute	Reconsolidation blockade	Anxiolytic 1 and 7 d old fear memories disrupted	Effect ↓ by AM251 but not WAY100635
Campos et al. [77]	WR	i.p.	**5** mg/kg, subchronic, daily/7 d	EPM following PS	Anxiolytic	Effects ↓ by IP WAY100635
Hsiao et al. [78]	WR	CeA	**1** μg/μl	REM sleep time EPM OF	↓ REM sleep suppression Anxiolytic Anxiolytic	NA
Gomes et al. [79]	WR	BNST	**15**, **30**, **60**nmol, acute	CFC	Anxiolytic	Both effects ↓ by intra-BNST WAY100635
El Batsh et al. [80]	LE-H R	i.p.	**10**mg/kg, chronic, daily/14 d	CFC	Anxiogenic	NA
Campos et al. [81]	C57BL/6 mice	i.p.	**30**mg/kg 2 h after CUS, chronic daily/14 d	EPM NSF	Anxiolytic Anxiolytic	Both effects ↓ by AM251
Do Monte et al. [82]	L-E HR	IL	1 μg or **0.4** μg/0.2 μl 5 min before extinction daily/4 d	Extinction of CFC	Anxiolytic	Effect ↓ by IP rimonabant
Campos et al. [83]	Rat	i.p.	**5**mg/kg, chronic, daily/21 d	ETM	Anxiolytic Panicolytic	Panicolytic effect ↓ by intra-dlPAG WAY100635
Almeida et al. [84]	Rat	i.p.	**1**, 5, 15 mg/kg, acute	SI	Anxiolytic	NA
Gomes et al. [85]	WR	BNST	**30** and 60 nmol, acute	RS	Anxiogenic ↑ Tachydardia	Effect ↓ by WAY100635
Twardowschy et al. [86]	SM	i.p.	**3**mg/kg, acute	PS	Panicolytic	Effects ↓ by IP WAY100635
Focaga et al. [87]	WR	PL	15, **30**, 60 nmol, acute	EPM EPM after RS CFC	Anxiogenic Anxiolytic Anxiolytic	All effects ↓ by intra PL WAY100635 Anxiolytic EPM effect post-RS ↓ by IP metyrapone
Nardo et al. [88]	SM	i.p.	**30** mg/kg, acute	MBT	Anticompulsive	NA
da Silva et al. [89]	WR	SNpr	**5** μg/**0.2** μl	$GABA_A$ blockade in dlSC	Panicolytic	Both effects ↓ by AM251

Effective doses are in bold

Receptor specific agents: AM251 = cannabinoid receptor type 1 (CB_1R) inverse agonist; WAY100635 = 5-hydroxytryptamine 1A antagonist; SR141716A = CB_1R antagonist; rimonabant = CB_1R antagonist; capsazepine = transient receptor potential vanilloid type 1 antagonist; naloxone = opioid antagonist; flumazenil = $GABA_A$ receptor antagonist

Anxiolytic effects in models used: CER = reduced fear response; CFC = reduced conditioned freezing; CFC extinction = reduced freezing following extinction training; EPM = reduced % time in open arm; ETM = decreased inhibitory avoidance; L-DT = increased % time in light; VCT = increased licks indicating reduced conflict; NSF = reduced latency to feed; OF = increased % time in center; SI = increased social interaction

Anticomplusive effects: MBT = reduced burying

Panicolytic effects: ETM = decreased escape; $GABA_A$ blockade in dlSC = defensive immobility, and explosive escape; PAG-E-Stim = increased threshold for escape; PS = reduced explosive escape

WR = Wistar rats; SM = Swiss mice; L-E HR = Long–Evans hooded rats; i.p. = intraperitoneal; dlPAG = dorsolateral periaqueductal gray; i.c.v. = intracerebroventricular; PL = prelimbic; IL = infralimbic; BNST = bed nucleus of the stria terminalis; CeA = amygdala central nucleus; SNpr = substantia nigra pars reticularis; CUS = chronic unpredictable stress; GSCT = Geller–Seifter conflict test; CER = conditioned emotional response; EPM = elevated plus maze; VCT = Vogel conflict test; CFC = contextual fear conditioning; RS = restraint stress; ETM = elevated T maze; PAG E-stim = electrical stimulation of the dlPAG; L-DT = light–dark test; SI = social interaction; OF = open field; MBT = marble-burying test; PS = predator stress; NSF = novelty suppressed feeding test; $GABA_A$ = γ-aminobutyric acid receptor A; dlSC = deep layers superior colliculus; REM = rapid eye movement; NA = not applicable

activation [79], and also upon microinjection into the central nucleus of the amygdala [78]. In the prelimbic cortex, which drives expression of fear responses via connections with the amygdala [94], CBD had more complex effects: in unstressed rats, CBD was anxiogenic in the EPM, partially via 5-HT_{1A}R receptor activation; however, following acute restraint stress, CBD was anxiolytic [87]. Finally, the anxiolytic effects of systemic CBD partially depended on $GABA_A$ receptor activation in the EPM model but not in the VCT model [61, 62].

As noted, CBD has been found to have a bell-shaped response curve, with higher doses being ineffective. This may reflect activation of TRPV1 receptors at higher dose, as blockade of TRPV1 receptors in the DPAG rendered a previously ineffective high dose of CBD as anxiolytic in the EPM [66]. Given TRPV1 receptors have anxiogenic effects, this may indicate that at higher doses, CBD's interaction with TRPV1 receptors to some extent impedes anxiolytic actions, although was notably not sufficient to produce anxiogenic effects.

Stress-induced Anxiety Models

Stress is an important contributor to anxiety disorders, and traumatic stress exposure is essential to the development of PTSD. Systemically administered CBD reduced acute increases in heart rate and blood pressure induced by restraint stress, as well as the delayed (24 h) anxiogenic effects of stress in the EPM, partially by 5-HT_{1A}R activation [67, 73]. However intra-BNST microinjection of CBD *augmented* stress-induced heart rate increase, also partially via 5-HT_{1A}R activation [85]. In a subchronic study, CBD administered daily 1 h after predator stress (a proposed model of PTSD) reduced the long-lasting anxiogenic effects of chronic predator stress, partially via 5-HT_{1A}R activation [77]. In a chronic study, systemic CBD prevented increased anxiety produced by chronic unpredictable stress, in addition to increasing hippocampal AEA; these anxiolytic effects depended upon CB_1R activation and hippocampal neurogenesis, as demonstrated by genetic ablation techniques [81]. Prior stress also appears to *modulate* CBD's anxiogenic effects: microinjection of CBD into the prelimbic cortex of unstressed animals was anxiogenic in the EPM but following restraint stress was found to be anxiolytic [87]. Likewise, systemic CBD was anxiolytic in the EPM following but not prior to stress [65].

PD and Compulsive Behavior Models

CBD inhibited escape responses in the ETM and increased DPAG escape electrical threshold [68], both proposed models of panic attacks [95]. These effects partially depended on 5-HT_{1A}R activation but were not affected by CB_1R blockade. CBD was also panicolytic in the predator–prey model, which assesses explosive escape and defensive immobility in response to a boa constrictor snake, also partially via 5-HT_{1A}R activation; however, more consistent with an anxiogenic effect, CBD was also noted to decrease time spent outside the burrow and increase defensive attention (not shown in Table 1) [75, 86] . Finally, CBD, partially via CB_1Rs, decreased defensive immobility and explosive escape caused by bicuculline-induced neuronal activation in the superior colliculus [89]. Anticompulsive effects of CBD were investigated in marble-burying behavior, conceptualized to model OCD [96]. Acute systemic CBD reduced marble-burying behavior for up to 7 days, with no attenuation in effect up to high (120 mg/kg) doses, and effect shown to depend on CB_1Rs but not 5-HT_{1A}Rs [71, 74, 88].

Contextual Fear Conditioning, Fear Extinction, and Reconsolidation Blockade

Several studies assessed CBD using contextual fear conditioning. Briefly, this paradigm involves pairing a neutral context, the conditioned stimulus (CS), with an aversive unconditioned stimulus (US), a mild foot shock. After repeated pairings, the subject learns that the CS predicts the US, and subsequent CS presentation elicits freezing and other physiological responses. Systemic administration of CBD prior to CS re-exposure reduced conditioned cardiovascular responses [63], an effect reproduced by microinjection of CBD into the BNST, and partially mediated by 5-HT_{1A}R activation [79]. Similarly, CBD in the prelimbic cortex reduced conditioned freezing [70], an effect prevented by 5-HT_{1A}R blockade [87]. By contrast, CBD microinjection in the infralimbic cortex *enhanced* conditioned freezing [70]. Finally, El Batsh et al. [80] reported that repeated CBD doses over 21 days, that is chronic as opposed to acute treatment, *facilitated* conditioned freezing. In this study, CBD was administered prior to conditioning rather than prior to re-exposure as in acute studies, thus further directly comparable studies are required.

CBD has also been shown to enhance extinction of contextually conditioned fear responses. Extinction training involves repeated CS exposure in the absence of the US, leading to the formation of a new memory that inhibits fear responses and a decline in freezing over subsequent training sessions. Systemic CBD administration immediately before training markedly enhanced extinction, and this effect depended on CB_1R activation, without involvement of TRPV1 receptors [65]. Further studies showed CB_1Rs in the infralimbic cortex may be involved in this effect [82].

CBD also blocked reconsolidation of aversive memories in rat [76]. Briefly, fear memories, when reactivated by re-exposure (retrieval), enter into a labile state in

which the memory trace may either be reconsolidated or extinguished [97], and this process may be pharmacologically modulated to achieve reconsolidation blockade or extinction. When administered immediately following retrieval, CBD prevented freezing to the conditioned context upon further re-exposure, and no reinstatement or spontaneous recovery was observed over 3 weeks, consistent with reconsolidation blockade rather than extinction [76]. This effect depended on CB_1R activation but not 5-$HT_{1A}R$ activation [76].

Summary and Clinical Relevance

Overall, existing preclinical evidence strongly supports the potential of CBD as a treatment for anxiety disorders. CBD exhibits a broad range of actions, relevant to multiple symptom domains, including anxiolytic, panicolytic, and anticompulsive actions, as well as a decrease in autonomic arousal, a decrease in conditioned fear expression, enhancement of fear extinction, reconsolidation blockade, and prevention of the long-term anxiogenic effects of stress. Activation of 5-$HT_{1A}Rs$ appears to mediate anxiolytic and panicolytic effects, in addition to reducing conditioned fear expression, although CB_1R activation may play a limited role. By contrast, CB_1R activation appears to mediate CBD's anticompulsive effects, enhancement of fear extinction, reconsolidation blockade, and capacity to prevent the long-term anxiogenic consequences of stress, with involvement of hippocampal neurogenesis.

While CBD predominantly has acute anxiolytic effects, some species discrepancies are apparent. In addition, effects may be contingent on prior stress and vary according to brain region. A notable contrast between CBD and other agents that target the eCB system, including THC, direct CB_1R agonists and FAAH inhibitors, is a lack of anxiogenic effects at a higher dose. Further receptor-specific studies may elucidate the receptor specific basis of this distinct dose response profile. Further studies are also required to establish the efficacy of CBD when administered in chronic dosing, as relatively few relevant studies exist, with mixed results, including both anxiolytic and anxiogenic outcomes.

Overall, preclinical evidence supports systemic CBD as an acute treatment of GAD, SAD, PD, OCD, and PTSD, and suggests that CBD has the advantage of not producing anxiogenic effects at higher dose, as distinct from other agents that enhance CB_1R activation. In particular, results show potential for the treatment of multiple PTSD symptom domains, including reducing arousal and avoidance, preventing the long-term adverse effects of stress, as well as enhancing the extinction and blocking the reconsolidation of persistent fear memories.

Human Experimental and Clinical Studies

Evidence from Acute Psychological Studies

Relevant studies are summarized in Table 2. The anxiolytic effects of CBD in humans were first demonstrated in the context of reversing the anxiogenic effects of THC. CBD reduced THC-induced anxiety when administered simultaneously with this agent, but had no effect on baseline anxiety when administered alone [99, 100]. Further studies using higher doses supported a lack of anxiolytic effects at baseline [101, 107]. By contrast, CBD potently reduces experimentally induced anxiety or fear. CBD reduced anxiety associated with a simulated public speaking test in healthy subjects, and in subjects with SAD, showing a comparable efficacy to ipsapirone (a 5-$HT_{1A}R$ agonist) or diazepam [98, 105]. CBD also reduced the presumed anticipatory anxiety associated with undergoing a single-photon emission computed tomography (SPECT) imaging procedure, in both healthy and SAD subjects [102, 104]. Finally, CBD enhanced extinction of fear memories in healthy volunteers: specifically, inhaled CBD administered prior to or after extinction training in a contextual fear conditioning paradigm led to a trend-level enhancement in the reduction of skin conductance response during reinstatement, and a significant reduction in expectancy (of shock) ratings during reinstatement [106].

Evidence from Neuroimaging Studies

Relevant studies are summarized in Table 3. In a SPECT study of resting cerebral blood flow (rCBF) in normal subjects, CBD reduced rCBF in left medial temporal areas, including the amygdala and hippocampus, as well as the hypothalamus and left posterior cingulate gyrus, but increased rCBF in the left parahippocampal gyrus. These rCBF changes were not correlated with anxiolytic effects [102]. In a SPECT study, by the same authors, in patients with SAD, CBD reduced rCBF in overlapping, but distinct, limbic and paralimbic areas; again, with no correlations to anxiolytic effects [104].

In a series of placebo-controlled studies involving 15 healthy volunteers, Fusar-Poli et al. investigated the effects of CBD and THC on task-related blood-oxygen-level dependent functional magnetic resonance imaging activation, specifically the go/no-go and fearful faces tasks [109, 110]. The go/no-go task measures response inhibition, and is associated with activation of medial prefrontal, dorsolateral prefrontal, and parietal areas [111]. Response activation is diminished in PTSD and other anxiety disorders, and increased activation predicts response to treatment [112]. CBD produced no changes in predicted areas (relative to placebo) but reduced activation in the left insula, superior temporal gyrus, and transverse temporal gyrus. The fearful faces task activates the amygdala, and other medial temporal areas involved in

Table 2 Human psychological studies

Study	Subjects, design	CBD route, dose	Measure	Effect
Karniol et al. [99]	HV, DBP	Oral, 15, 30, 60 mg, alone or with THC, acute, at 55, 95, 155, and 185 min	Anxiety and pulse rate after THC and at baseline	↓ THC-induced increases in subjective anxiety and pulse rate No effect at baseline
Zuardi et al., [100]	HV, DBP	Oral 1 mg/kg alone or with THC, acute, 80 min	STAI score after THC	↓ THC-induced increases in STAI scores
Zuardi et al. [98]	HV, DBP	Oral 300 mg, acute, 80 min	VAMS, STAI and BP following SPST	↓ STAI scores ↓ VAMS scores ↓ BP
Martin-Santos et al. [101]	HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	Baseline anxiety and pulse rate	No effect
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	VAMS before SPECT SPECT	↓ VAMS scores
Bhattacharyya et al. [103]	15 HV DBP	Oral 600 mg, acute, 1, 2, 3 h	STAI scores VAMS scores	↓ STAI scores ↓ VAMS scores
Crippa et al. [104]	SAD and HC DBP	Oral 400 mg, acute, 75 and 140 min	VAMS before SPECT SPECT	↓ VAMS scores
Bergamaschi et al. [105]	SAD and HC DBP	Oral 600 mg, acute, 1, 2, 3 h	VAMS, SSPS-N, cognitive impairment, SCR, HR after SPST	↓ VAMS, SSPS-N and cognitive impairment, no effect on SCR or HR
Das et al. [106]	HV DBP	Inhaled, 32 mg, acute, immediately following, before, after extinction	SCR and shock expectancy following extinction	CBD after extinction training produced trend level reduction in SCR and decreased shock expectancy
Hindocha et al. [107]	Varying in schizotypy and cannabis use, DBP	Inhaled, 16 mg, acute	Baseline VAS anxiety	No significant effect of CBD

HV = healthy volunteers; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; THC = $^{\Delta}$9-tetrahydrocannabinol; STAI = Spielberger's state trait anxiety inventory; VAMS = visual analog mood scale; BP = blood pressure; SPST = simulated public speaking test; SCR = skin conductance response; SPECT = single-photon emission computed tomography; SSPS-N = negative self-evaluation subscale; HR = heart rate; VAS = visual analog scale, CBD = cannabidiol

Table 3 Neuroimaging studies

Study	Subjects, design	CBD route, dose, timing	Measure	Effect of CBD
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	SPECT, resting (rCBF)	↓ rCBF in left medial temporal cluster, including amygdala and HPC, also ↓ rCBF in the HYP and posterior cingulate gyrus ↑ rCBF in left PHG
Borgwardt et al. [108]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI during oddball and go/no-go task	↓ Activation in left insula, STG and MTG
Fusar-Poli et al. [109]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI activation during fearful faces task	↓ Activation in left medial temporal region, including amygdala and anterior PHG, and in right ACC and PCC
Fusar-Poli et al. [110]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI functional connectivity during fearful faces task	↓ Functional connectivity between L) AMY and ACC
Crippa et al. [104]	SAD and HC DBP	Oral 400 mg, acute, 75 and 140 min	SPECT, resting (rCBF)	↓ rCBF in the left PHG, HPC and ITG. ↑ rCBF in the right posterior cingulate gyrus

CBD = cannabidiol; HV = healthy controls; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; SPECT = single-photo emission computed tomography; rCBF = regional cerebral blood flow; fMRI = functional magnetic resonance imaging; HPC = hippocampus; HYP = hypothalamus; PHG = parahippocampal gyrus; STG = superior temporal gyrus; MTG = medial temporal gyrus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex

emotion processing, and heightened amygdala response activation has been reported in anxiety disorders, including GAD and PTSD [113, 114]. CBD attenuated blood-oxygen-level dependent activation in the left amygdala, and the anterior and posterior cingulate cortex in response to intensely fearful faces, and also reduced amplitude in skin conductance fluctuation, which was highly correlated with amygdala activation [109]. Dynamic causal modeling analysis in this data set further showed CBD reduced forward functional connectivity between the amygdala and anterior cingulate cortex [110].

Evidence from Epidemiological and Chronic Studies

Epidemiological studies of various neuropsychiatric disorders indicate that a higher CBD content in chronically consumed cannabis may protect against adverse effects of THC, including psychotic symptoms, drug cravings, memory loss, and hippocampal gray matter loss [115–118] (reviewed in [119]). As THC acutely induces anxiety, this pattern may also be evident for chronic anxiety symptoms. Two studies were identified, including an uncontrolled retrospective study in civilian patients with PTSD patients [120], and a case study in a patient with severe sexual abuse-related PTSD [121], which showed that chronic cannabis use significantly reduces PTSD symptoms; however, these studies did not include data on the THC:CBD ratio. Thus, overall, no outcome data are currently available regarding the chronic effects of CBD in the treatment of anxiety symptoms, nor do any data exist regarding the potential protective effects of CBD on anxiety potentially induced by chronic THC use.

Summary and Clinical Relevance

Evidence from human studies strongly supports the potential for CBD as a treatment for anxiety disorders: at oral doses ranging from 300 to 600 mg, CBD reduces experimentally induced anxiety in healthy controls, without affecting baseline anxiety levels, and reduces anxiety in patients with SAD. Limited results in healthy subjects also support the efficacy of CBD in acutely enhancing fear extinction, suggesting potential for the treatment of PTSD, or for enhancing cognitive behavioral therapy. Neuroimaging findings provide evidence of neurobiological targets that may underlie CBD's anxiolytic effects, including reduced amygdala activation and altered medial prefrontal amygdala connectivity, although current findings are limited by small sample sizes, and a lack of independent replication. Further studies are also required to establish whether chronic, in addition to acute CBD dosing is anxiolytic in human. Also, clinical findings are currently limited to SAD, whereas preclinical evidence suggests CBD's potential to treat multiple symptom domains relevant to GAD, PD, and, particularly, PTSD.

Conclusions

Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders, including PTSD, GAD, PD, OCD, and SAD, with a notable lack of anxiogenic effects. CBD's anxiolytic actions appear to depend upon CB_1Rs and 5-HT_{1A}Rs in several brain regions; however, investigation of additional receptor actions may reveal further mechanisms. Human experimental findings support preclinical findings, and also suggest a lack of anxiogenic effects, minimal sedative effects, and an excellent safety profile. Current preclinical and human findings mostly involve acute CBD dosing in healthy subjects, so further studies are required to establish whether chronic dosing of CBD has similar effects in relevant clinical populations. Overall, this review emphasizes the potential value and need for further study of CBD in the treatment of anxiety disorders.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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REVIEW

Use of cannabidiol in anxiety and anxiety-related disorders

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ABSTRACT

Objective: Cannabidiol (CBD) has a proposed novel role in the management of anxiety owing to its actions on the endocannabinoid system. The purpose of this systematic review was to evaluate the current evidence on the safety and efficacy of CBD in anxiety and anxiety-related disorders.
Data sources: A literature search was conducted on PubMed, Google Scholar, and International Pharmaceutical Abstracts from database inception through June 2019. A bibliographic search of relevant articles was also conducted.
Study selection: Articles published from case reports, case series, or randomized controlled trials on human subjects were included in the review if they examined the safety and efficacy of CBD therapy in anxiety and anxiety-related disorders.
Data extraction: Two reviewers independently extracted the following data from the articles: year of publication; study design; patient characteristics (sex; type of anxiety disorder; use of concomitant anxiolytic therapy); dosing strategy and route of CBD administration; and safety and efficacy outcomes.
Results: Eight articles were included in the review: 6 small, randomized controlled trials; 1 case series; and 1 case report. These studies examined the role of CBD in the anxiety response of healthy volunteers; in generalized anxiety disorder; in social anxiety disorder; and in the anxiety component of posttraumatic stress syndrome. No articles that evaluated CBD in panic disorder, specific phobia, separation anxiety, and obsessive-compulsive disorder were identified. In the studies, CBD was administered orally as a capsule or as a sublingual spray and as either monotherapy or adjunctive therapy. Doses varied widely, with studies employing fixed CBD doses ranging from 6 mg to 400 mg per dose. Various anxiety assessment scales were used in the studies to assess efficacy, with CBD demonstrating improved clinical outcomes among the instruments. In general, CBD was well-tolerated and associated with minimal adverse effects, with the most commonly noted adverse effects being fatigue and sedation.
Conclusion: CBD has a promising role as alternative therapy in the management of anxiety disorders. However, more studies with standardized approaches to dosing and clinical outcome measurements are needed to determine the appropriate dosing strategy for CBD and its place in therapy.

Background

Anxiety is an adaptive, emotional response that naturally occurs as a result of a perceived threat.[1] Anxiety becomes maladaptive when it occurs excessively or inappropriately in the absence of relevant threatening stimuli.[1] The exact pathophysiology of anxiety-related disorders is unknown. However, results from neuroimaging and biochemical studies suggest that the variation between adaptive and maladaptive anxiety responses is modulated by regions of the limbic system—primarily the amygdala—and key neurotransmitters, such as dopamine (DA), norepinephrine (NE), γ-aminobutyric acid (GABA), and serotonin (5-HT).[2]

Within *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobia (SP), and separation anxiety are classified as anxiety disorders. Obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) share a common symptomatology of excessive anxiety; however, they are reviewed in their own respective chapters within *the DSM-5*, after the

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Key Points

Background:

- As a group, anxiety disorders and anxiety-related disorders are the most common psychiatric conditions in the United States. As such, they pose a serious disease burden to patients and the health care system because of decreased well-being, physical impairment, loss of productivity, and increased health care utilization costs.
- At present, the mainstay agents for treatment of anxiety have limitations in efficacy and are associated with a number of adverse effects, which suggests the need for new pharmacotherapies for these disorders.
- Cannabidiol (CBD) is a nonhallucinogenic chemical compound, derived from the plant *Cannabis sativa*, with a novel role in the management of anxiety.
- This article provides a review of evidence on the clinical efficacy and safety of CBD used to manage anxiety and anxiety-related disorders.

Findings:

- In the studies reviewed, CBD consistently demonstrated improved clinical outcomes in anxiety disorders, with a minimal adverse-effect profile.
- However, optimal dose, route of administration, and dosing strategy (acute vs. chronic use) of CBD in the management of anxiety disorders remain undetermined.
- Pharmacists have an essential role in advising patients and prescribers on the use of alternative therapies. Given the heightened popularity of CBD, it is crucial that pharmacists are knowledgeable about its benefits and are able to provide appropriate recommendations on the place in therapy of CBD in the treatment of common disorders, such as anxiety.

chapter on anxiety disorders. As a group, the anxiety disorders and anxiety-related disorders of PTSD and OCD are the most common psychiatric conditions in the United States.[3] Taken together, these disorders have an estimated lifetime prevalence of approximately 29% for U.S. adults.[3,4] As such, they pose a substantial disease burden to patients and the health care system because of their association with decreased well-being, physical impairment, loss of productivity, and increased health care utilization costs.[3,4]

At present, the primary pharmacologic treatment for anxiety and anxiety-related disorders involves the use of medications that modulate the activity of DA, NE, GABA, and 5-HT neurotransmitters. Benzodiazepines are prescribed commonly because of their modulation of GABA. Likewise, antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, 5-HT receptor antagonists, monoamine oxidase inhibitors, and buspirone are frequently used for their effects on DA, NE, and 5-HT. Less commonly prescribed agents for anxiety and anxiety-related disorders include second generation antipsychotics, anticonvulsants, and certain antihistamines, such as hydroxyzine. These pharmacotherapies have limitations in efficacy and are associated with a number of adverse effects (e.g., sexual dysfunction and potential for dependence and tolerance), which suggests the need for novel therapeutic modalities for management of anxiety and anxiety-related disorders.[5-7]

The endocannabinoid system (ECS) is a promising therapeutic target for anxiolytic-drug development owing to its purported role in modulating synaptic plasticity and neuronal activity involved in the anxiety response.[4,5,8-12] Primary activity of signaling within the ECS is thought to be because of the action on 2 known cannabinoid receptors, CB1 and CB2.[4,5,8-12] Cannabidiol (CBD), a chemical compound known as a phytocannabinoid, is derived from the plant *Cannabis sativa* and may have a role in the management of anxiety given its pharmacologic activity within the ECS.[4,5,8-12] Among the more than 400 chemicals produced by *C sativa*, delta-9-tetrahydrocannabinol (THC) and CBD are the major compounds.[4,5,8-12] THC is the most abundant psychoactive chemical and is primarily responsible for the well-known hallucinogenic effects of *C sativa*. In contrast, CBD is not psychoactive.[4,5,8-12]

In the literature, CBD has several proposed therapeutic effects accomplished through multiple mechanisms. Despite low affinity for CB1 and CB2 receptors, CBD has proposed indirect activity on the ECS through its action of inhibiting the inactivation of anandamide—a neurotransmitter within the ECS—which leads to activity on the CB1 receptor.[4,5,8-12] This mechanism, in conjunction with activity on 5-HT_{1A} receptors, is believed to be a key factor in the reported therapeutic effects of CBD in anxiety.[4,5,8-12] Available literature suggests a favorable adverse-effect profile of CBD and minimal drug interaction potential when compared with other therapeutic agents; however, it should be noted that there is a dearth of studies examining these parameters.[13]

CBD can be administered through various routes of administration and is currently available and marketed in numerous formulations, such as tinctures administered under the tongue, concentrated oil administered orally or topically, topical compounds such as ointments and creams, vaporized solutions, and infused beverages and food items. In the United States, there is only 1 Food and Drug Administration (FDA)-approved CBD product, Epidiolex, which is approved for treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.[14] All other cannabis-derived CBD products remain under the purview of the FDA regulation under the 2018 Farm Bill, and determination of the scope of this regulation is evolving.[15] With the dramatic increase in use of CBD products, it is prudent to assess the validity of therapeutic claims as well as the safety profile.[15] This information will be beneficial to clinicians when examining the risks and benefits of using CBD for pharmacologic activity in anxiety.

Objective

The purpose of this systematic review was to evaluate the current evidence on the safety and efficacy of CBD in the management of anxiety and anxiety-related disorders.

Methods

Data sources

This study was a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance statement.[16] A free text search of PubMed (January 1996-June 2019) was conducted. The term "cannabidiol" was combined with either "generalized anxiety disorder," or "social anxiety disorder," or "panic disorder," or "specific phobia," or "separation anxiety," or "post-traumatic stress disorder," or "obsessive compulsive disorder" with the Boolean operator AND. This free text search was duplicated on Google Scholar and International Pharmaceutical Abstracts. In addition, references of relevant articles were also reviewed.

Study selection

Articles were included in the review if they examined CBD treatment in diagnosed anxiety or anxiety-related disorders or if they evaluated the anxiety response in healthy volunteers. Animal studies, articles evaluating the psychosis components of PTSD and OCD, and studies evaluating the role of CBD in managing THC-related anxiety were excluded from review. In addition, editorials, commentaries, and letters to the editor were excluded. Two reviewers independently executed the search and screened articles for inclusion.

Data extraction

Two reviewers independently extracted the following data from the articles: year of publication; study design; patient characteristics (sex; type of anxiety disorder; use of concomitant anxiolytic therapy); dosing strategy and route of CBD administration; and safety and efficacy outcomes. Efficacy outcomes included scores on assessment scales for anxiety, such as the Screen for Anxiety-Related Disorders (SCARED), Hamilton Anxiety Rating Scale (HAM-A), Visual Analogue Mood Scale (VAMS), State-Trait Anxiety Inventory (STAI), Bodily Symptoms Scale (BSS), and Negative Self-Statements subscale (SSPS-N).

Results

Study characteristics

A total of 233 potentially relevant articles resulted from the search. Eight articles met criteria for full text review: 6 small, randomized controlled trials; 1 case series; and 1 case report (Figure 1). One article evaluating the role of CBD in the anxiety response of healthy volunteers, 1 assessing CBD in GAD, 1

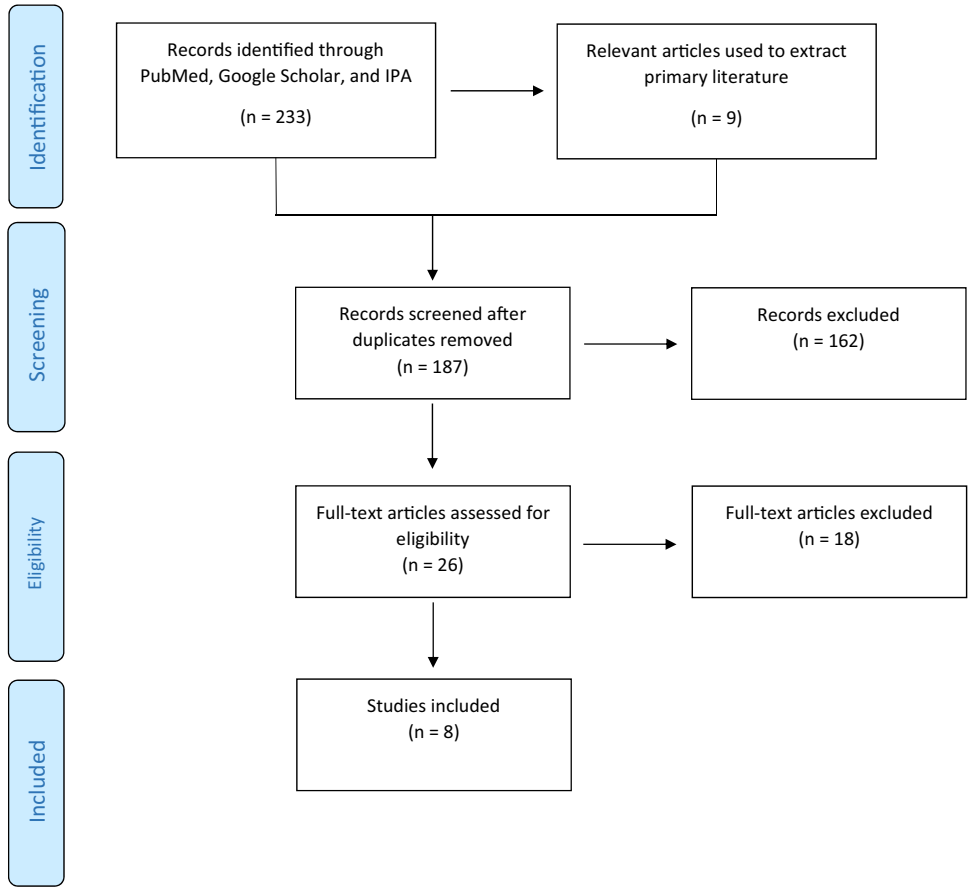

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram. Abbreviation used: IPA, International Pharmaceutical Abstracts.

evaluating CBD in the anxiety response of PTSD, and 5 articles examining CBD in SAD were identified. No articles on the role of CBD in PD, SP, separation anxiety, or OCD management met the criteria for review. Table 1 summarizes the efficacy and safety outcomes of the studies.

Anxiety response in healthy volunteers: Effects of CBD on regional cerebral blood flow

Crippa et al.[17] conducted a double-blind, crossover study in 10 healthy male patients to evaluate the effect of CBD on neural activity of pathways that normally mediate anxiety, measured through neuroimaging. None of the patients nor their first-degree relatives had a history of psychiatric illness. The participants were separated into 2 groups of 5. Regional cerebral blood flow (rCBF) was measured at rest via single-photon emission computed tomography (SPECT), and each participant was evaluated on 2 occasions separated by 1 week. At the first session, 1 group received 400 mg of CBD while the other group received placebo, both administered as a gelatin capsule in double-blinded fashion. After 90 minutes, SPECT images were taken. In the second session, the procedure was repeated in a crossover design with those who received placebo being administered CBD and vice versa. VAMS was used to assess subjective feelings of anxiety along with physical sedation, mental sedation, and other attitudes and perceptions. VAMS scores were assessed at 30 minutes before CBD or placebo ingestion, at the time of ingestion, and at 60 and 75 minutes following ingestion. A significant reduction in subjective anxiety, measured through VAMS, was noted following CBD administration at all measurements ($P < 0.001$). In the investigators' comparison of rCBF measurements between CBD and placebo ingestion groups, a significantly ($P < 0.001$) increased uptake of the injected ethyl-cisteinate dimer into the medial temporal cortex along with VAMS findings

Table 1
Study summaries: Efficacy and safety of CBD in anxiety disorders

Citation	N	Classification	Study design	Subject(s)	CBD dose and route of administration	Acute versus chronic CBD dosing	Comparison anxiolytic with or without placebo	Measures of anxiety symptoms
Crippa et al., 2004[17]	10	Anxiety response in healthy volunteers	RCT; crossover	Healthy males without anxiety diagnosis	CBD 400 mg orally x 1 dose, gelatin capsules (n = 10)	Acute	Placebo comparison with crossover (n = 10)	VAMS
Shannon et al., 2019[19]	72	Anxiety response in patients with either GAD or insomnia diagnosis	Open-label, case series	GAD diagnosis (n = 47; 28 males; 19 females) Insomnia diagnosis (n = 25)	CBD 25–175 mg, dosed daily, oral capsules (n = 72)	Chronic	None	HAM-A
Shannon et al., 2016[20]	1	GAD	Case report	10-year-old female with anxiety diagnosis	Months 1–4: CBD 25 mg dosed daily, capsule Months 4–6: CBD 25 mg dosed daily, capsule; and CBD 6–12 mg as needed for anxiety, sublingual spray	Chronic and acute	None	SCARED
Zuardi et al., 2017[21]	59	Healthy volunteer model of SAD	RCT	Healthy males (n = 29) and females (n = 30)	CBD oral capsule x 1 dose: 100 mg (n = 11; 5 males, 6 females) 300 mg (n = 12; 6 males, 6 females) 900 mg (n = 12; 6 males, 6 females)	Acute	Placebo (n = 12; 6 males, 6 females) Clonazepam 1 mg (n = 12; 6 males, 6 females)	VAMS
Zuardi et al, 1993[23]	40	Healthy volunteer model of SAD	RCT	Healthy males (n = 18) and females (n = 22)	CBD 300 mg, oral gelatin capsule x 1 dose (n = 10)	Acute	Placebo (n = 10) Ipsapirone 5 mg (n = 10) Diazepam 10 mg (n = 10)	VAMS
Linares et al, 2019[24]	57	Healthy volunteer model of SAD	RCT	Healthy males	CBD oral capsule x 1 dose: 150 mg (n = 15) 300 mg (n = 15) 600 mg (n = 12)	Acute	Placebo (n = 15)	VAMS
Bergamaschi et al, 2011[25]	36	SAD diagnosis	RCT	SAD diagnosis (n = 24; 12 males, 12 females) Healthy control patients (n = 12; 6 males, 6 females)	CBD 600 mg x 1 dose, oral gelatin capsules (n = 12)	Acute	Placebo (n = 12; 6 males, 6 females)	VAMS
Crippa et al., 2011[26]	10	SAD diagnosis	RCT; crossover	Males with SAD diagnosis	CBD 400 mg oral x 1 dose, gelatin capsules (n = 10)	Acute	Placebo comparison with crossover (n = 10)	VAMS

Abbreviations used: CBD, cannabidiol; RCT, randomized controlled trial; VAMS, Visual Analogue Mood Scale; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; SCARED, Screen for Anxiety-Related Disorders; SAD, social anxiety disorder.

Table 2
Considerations for CBD

Potential benefit	Potential risks	
Efficacy	Product variability	Drug interactions
Studies have found CBD to be an effective alternative therapy in the acute treatment of anxiety disorders, specifically:	CBD is considered a dietary supplement, and thus lacks standardization in the following areas:	Potential CYP450 interactions: CBD has been found to be a potent inhibitor of CYP3A4 and CYP2D6, increasing the serum level of the following medications:
• GAD	• Dose-effect response	• Warfarin
• SAD	• Dosage strength	• Macrolides
• Anxiety related to PTSD	• Route of administration	• Calcium channel blockers
	• Purity	• Antiretrovirals
	• Regulation	• Antidepressants
	• Product manufacturing	• Antipsychotics
CBD has shown minimal adverse effects compared with existing pharmacotherapy for acute anxiety.	• Labeling	• Opioids
	• Patient access	It is important to consider patients with potential genetic polymorphisms of CYP450 enzymes:
	• Legal status	• Decreased CYP2C19 or CYP3A4 have potential risk of CBD accumulation.

Abbreviations used: CBD, cannabidiol; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PTSD, posttraumatic stress disorder.

supported the a priori hypothesis that the limbic and paralimbic areas in the brain are likely mediators of CBD's anxiolytic effect. The study results support findings of another study, which found the role of CBD in GAD to occur owing to effects on the limbic and paralimbic regions of the brain.[18] Crippa et al.[17] noted sedation as an observed adverse effect of CBD in the study but did not expound on the magnitude or frequency of this reported effect.

GAD: CBD in anxiety and sleep

Shannon et al.[19] evaluated the use of open-label CBD therapy on anxiety and sleep levels in a case series of 72 adults seen at a psychiatric outpatient clinic over a 3-month timeframe. Patients were included in the study if they had either a diagnosis of anxiety or a sleep disorder and had at least 1 follow-up visit in the clinic after CBD was prescribed. Patients were excluded if they had a sole or primary diagnosis of schizophrenia, PTSD, or agitated depression. Use of other psychoactive medications and adjunctive counseling services did not preclude participation in this study. Patients' anxiety was assessed through the use of validated HAM-A. On HAM-A, anxiety scores range from 0 to 56, with a score below 17 being indicative of mild anxiety and a score above 25 indicating severe anxiety. Safety was assessed through spontaneous self-report in this study. Patients received CBD in fixed doses, ranging from 25 mg/d to 175 mg/d, with the majority of patients receiving the 25-mg daily dose. All patients completed the 1-month follow-up assessment of HAM-A, whereas 56.9% and 37.5% followed up at the 2- and 3-month timeframes for HAM-A, respectively. At the 1-month assessment, the majority of patients (79.2%) experienced an improvement in anxiety based on HAM-A scores. Of those who followed up at the 2-month assessment, 78.1% demonstrated an improvement in anxiety compared with the prior 1-month visit. There was no appreciable difference in mean HAM-A scores between the 2-month and 3-month follow-up assessments (mean HAM-A scores of 16.35 and 16.36, respectively). A few adverse effects were reported in this study: dry eyes, mild sedation, fatigue, and an increase in sexually inappropriate behaviors. The patients who experienced mild sedation reported resolution within the first weeks of treatment. Furthermore, a small percentage of patients who experienced fatigue or an increase in sexually inappropriate behavior discontinued therapy. The authors concluded that anxiety scores decreased over the course of the study, and the clinical effect on anxiety was maintained throughout the study duration. CBD was well-tolerated and associated with very few instances of treatment discontinuation.

Anxiety response in PTSD: Effectiveness of CBD oil for pediatric anxiety and insomnia as PTSD

A case report by Shannon et al.[20] evaluated the effectiveness of CBD oil in anxiety and sleep disorder secondary to PTSD in a 10-year-old girl. The girl had previously been treated with ineffective pharmacotherapy and had experienced adverse effects from the medication. CBD, administered initially as a capsule and subsequently as a sublingual spray for as-needed dosing, was used for the patient's anxiety and insomnia. The patient was also receiving eicosapentaenoic acid fish oil and diphenhydramine with CBD therapy. The patient was originally initiated on a CBD 25-mg capsule dosed daily, which she took for a duration of 4 months as monotherapy. After 4 months, the patient was prescribed adjunct CBD, administered as an as-needed sublingual spray and dosed at 6-12 mg per spray for breakthrough anxiety symptoms. The patient's anxiety was evaluated using SCARED, with a score above 25 indicating a childhood anxiety disorder. A SCARED score was evaluated before initiation of CBD and then monthly for an additional 5 months, for a total of 6 measurements. From baseline to sixth evaluation, the patient's SCARED score decreased from 34 to 18, a 47.06% reduction. No adverse effects of CBD were reported in this case report. The authors concluded that CBD oil may be an effective option to consider when attempting to reduce anxiety secondary to PTSD.

Healthy volunteer models of SAD: Anxiolytic effect of CBD during public speaking in real life

In this double-blinded study, Zuardi et al.[21] tested the hypothesis that increasing CBD doses would produce anxiolytic

effects in patients with anxiety. Fifty-nine healthy men and women within the age range of 18-35 years were selected for the study. These patients had no diagnosed anxiety disorder, and no disorders involving alcohol or other substance abuse. However, the study was set up to test anxiety levels in public speaking scenarios as a manifestation of SAD. The volunteers were randomly assigned to 5 groups of 12 participants. Each volunteer received either 1 of 3 doses of CBD capsules (100 mg, 300 mg, or 900 mg), clonazepam 1-mg tablet, or placebo in a double-blinded randomized design. VAMS was used in this study to evaluate anxiety levels as well as the sedative effects of CBD. To assess physiological measurements, systolic blood pressure (BP), diastolic BP, and heart rate were recorded. In the procedure, 1 participant was instructed to speak in front of their group. The other participants who were not speaking at the time were instructed to remain silent with a neutral expression. Each member in the group would take their turn to speak. Each participant's VAMS anxiety and sedation score, BP, and heart rate were recorded at baseline, before the speech, during the middle of the speech, and after the speech. Data were compared at the varying time phases. VAMS scores of subjective anxiety were noted to be significantly decreased when the CBD 300-mg group was compared with the placebo and CBD 100-mg groups during the postspeech phase ($P < 0.05$). Similarly, a significantly greater decrease in VAMS was noted in the comparison of the CBD 300-mg group with the CBD 900-mg group in the speech phase ($P < 0.05$). Higher sedative effects were noted with clonazepam in comparison with the CBD and placebo groups among the phases ($P < 0.05$). The authors concluded that the CBD 300-mg dose had a greater therapeutic effect on anxiety when compared with the 100-mg and 900-mg doses. These results confirmed prior study findings and suggested that CBD induces acute anxiolytic effects with an inverted U-shaped dose-response curve in humans—an effect that, at this time, is not fully understood and should not be considered as an absolute pharmacodynamics principle.[21,22]

Effects of ipsapirone and CBD on human experimental anxiety

In a double-blinded study, Zuardi et al.[23] used 40 healthy subjects separated into 4 groups of 10 who received either oral CBD 300 mg, diazepam 10 mg, ipsapirone 5 mg, or placebo. The volunteers were subjected to a simulated public speaking test (SPST) to compare the anxiolytic properties of the assigned drug. The effects of these drugs were measured using VAMS, STAI, and BSS, which evaluates somatic symptoms (fatigue, weakness) that would indirectly affect anxiety. After a 15-minute adaptation period, baseline measures were collected before the intervention (drug or placebo) was given. One hour and 20 minutes after the drug was taken, prestress measures were collected. After collection, the subjects watched a video with instructions about the task they would be performing. Each subject had 2 minutes to prepare a 4-minute speech about a topic covered previously in a university course and was told the speech would be recorded and analyzed by a psychologist. Anticipatory anxiety measurements were taken before the subject began speaking. During the middle of the speech, researchers interrupted the subject and subjective anxiety measurements were collected. Fifteen minutes after the speech ended, poststress measurements were collected. The VAMS results of the study demonstrated that there was a significant increase in subjective anxiety in all groups ($P < 0.001$) during the SPST procedure. Diazepam significantly decreased subjective anxiety throughout the study when compared with placebo ($P = 0.016$). Specifically, diazepam decreased prestress ($P = 0.042$) and poststress ($P = 0.002$) measurements. However, diazepam also significantly increased feelings of physical sedation at the prestress ($P = 0.036$) and anticipatory anxiety ($P = 0.003$) measurements. Ipsapirone significantly decreased performance anxiety ($P = 0.037$) measurements when compared with placebo, while CBD significantly decreased poststress anxiety ($P = 0.017$) measurements. Only diazepam showed significant physical and mental sedative effects, which may limit its therapeutic application in some patients. The authors concluded that acute administration of CBD or ipsapirone may have beneficial alternative anxiolytic effects when used in healthy subjects and may be appropriate alternatives for those experiencing sedative effects from other anxiolytic medications.

CBD presents an inverted U-shaped dose-response curve in a SPST

Linares et al.[24] conducted a double-blind, placebo-controlled trial of 57 healthy adult males who were randomized to receive either placebo or CBD dosed at 150 mg, 300 mg, or 600 mg daily before SPST. The SPST was administered according to the Bergamaschi procedures.[25] VAMS was used to assess subjective anxiety. In the analysis of variance test of group comparisons, there were no significant findings among groups and phases of the SPST ($P = 0.1$). A post hoc analysis among groups during the phases of SPST indicated that patients in the CBD 300-mg group demonstrated lower anxiety levels in the speech phase than the placebo group ($P = 0.042$). The study investigators inferred an inverted U-shaped dose-response curve based on VAMS results with sequential CBD doses, with the 150-mg and 600-mg doses associated with minimal anxiolytic effects and the intermediate 300-mg dose producing the most clinically significant outcome on anxiety. This result supports findings from previous studies.[21-23] No safety outcomes were reported in this study.

SAD: CBD reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients

In a double-blind, randomized, controlled clinical trial, Bergamaschi et al.[25] compared the effects of taking oral CBD 600 mg with those of taking placebo in SPST. A total of 36 patients were included in the study; 24 were treatment-naive patients with SAD and 12 served as healthy controls (HCs) who did not receive medications. Of the 24 treatment-naive patients with SAD, 2 separate groups of 12 were formed randomly. One group received CBD while the other received placebo, both packed in identical gelatin capsules. Subjective ratings using VAMS, SSPS-N, and physiological measures such as BP, heart rate, and skin conductance were all measured at 6 different time points during SPST. The time points of evaluation were selected for full evaluation of anxiolytic effects seen with CBD compared with those seen with placebo. In the first stage of the procedure, a single dose of CBD or placebo was administered in a double-blind fashion along with administration of baseline measurements. In the second phase, participants were given instructions to prepare a 2- to 4-minute speech that would be videotaped and analyzed by a

psychologist. Researchers collected anticipatory speech measurements before the public speaking occurred. Interruptions in the speech were made in the middle and speech measurements were again taken. The speech was allowed to continue for another 2 minutes and then concluded, and 2 postspeech measurements were made 15 minutes and 35 minutes after the speech. After analyzing the results from the study, the VAMS scale showed that the placebo group presented with significantly higher anxiety levels with greater cognitive impairment, discomfort, and alertness as compared with the HCs. The pretreated CBD SAD group had significantly reduced anxiety, cognitive impairment, and discomfort during the speech performance compared with the placebo group ($P = 0.009$). An important observation made by the authors was that negative self-evaluation was almost abolished by CBD. There were no significant differences found in vital signs. Overall, the effects of single dose CBD in patients experiencing SAD show a promising impact with a rapid-onset therapeutic effect.

Neural basis of anxiolytic effects of CBD in generalized SAD

In a double-blinded preliminary report, whose purpose was to confirm the hypothesis that CBD may be effective in treating SAD, Crippa et al.[26] assessed 10 men with generalized SAD, which was confirmed by the structured clinical interview (SCID) for *DSM-IV*. All the subjects in the study were determined to have a severe social phobia. To analyze the effects of CBD in these patients, researchers evaluated each subject using the VAMS assessment. During the test, subjective ratings on VAMS were made 30 minutes before the ingestion of the drug (prestress), at the time of drug ingestion (adaptation), and at 75 minutes after ingestion (poststress). Functional neuroimaging was used to determine the neurophysiologic effect of CBD in patients with SAD. SPECT imaging was used to compare the effects of CBD and placebo on rCBF. This process was completed in a double-blind, randomized, repeated measures, within-subject crossover design using a dose of 400 mg of CBD given in oral gelatin capsules. In the first session, the men were given CBD 400 mg or placebo. In the second session, this exercise was performed again, but this time the men who had received CBD earlier were administered the placebo and vice versa.

Upon analysis of the VAMS score, the study showed that acute administration of CBD reduced subjective anxiety in patients clinically diagnosed with an anxiety disorder, in this case SAD. Specifically, CBD showed a significantly faster time onset of decreasing anxiety ($P < 0.001$) in the patient compared with placebo. Based on the VAMS score numbers, those taking CBD began with a mean assessment at prestress anxiety of 48.3 and ended poststress anxiety with 30.8, a decrease of 36.23%. Patients in the placebo group began prestress at an anxiety level of 46.9 and ended with a poststress anxiety level of 42.1, a decrease of only 10.23%. The SPECT imaging was able to show that CBD was active in the paralimbic and limbic areas. Overall, the authors concluded that CBD has important advantages in treatment of SAD, such as a minimal adverse-effect profile and early onset of action. However, the authors also concluded that more double-blind, placebo-controlled studies are needed to evaluate the long-term effects of CBD for treatment of anxiety disorders. Last, investigators suggested the need for further research and definitive conclusions on whether a relationship exists between rCBF and CBD plasma levels, which would potentially provide a less invasive strategy for monitoring CBD's clinical effects.

Discussion

CBD has been studied for use in treating anxiety-like responses for more than a decade.[27] Several early studies evaluated the use of CBD in preventing neural responses to fearful faces.[28,29] Initial studies evaluating the difference in response between CBD and THC showed that while THC use often results in negative behavioral and psychological effects, CBD is safe and well-tolerated with no difference from placebo in regard to increasing unwanted anxiety, sedation, positive psychotic symptoms, and intoxication.[28,30,31] In addition, CBD may even have utility in minimizing the negative effects of THC.[32]

On the basis of the results of currently available published human studies, it is seen that CBD has demonstrated a developing role as an alternative therapy in the indications of anxiety disorders, specifically GAD, SAD, and anxiety related to PTSD. Because the majority of the reviewed studies had small sample sizes, low statistical power posed a notable limitation. Primarily adult, male patients were enrolled in the studies, with only 1 pediatric case report meeting criteria for review. In addition, several studies enrolled healthy volunteers modeling varying anxiety disorders. Very few studies that enrolled patients with an anxiety diagnosis and compared the outcomes of taking CBD with those of taking placebo were identified. Taken together, these overall study characteristics may limit the generalizability of results. Similarly, because wide ranges of CBD doses were implemented among the studies, future evaluations of more intermediate range CBD doses may be warranted to determine optimal dosing definitively. Last, many studies made conclusions related to the dose-response curve of CBD on the basis of the results of neuroimaging findings and subjective scores on anxiety assessments without assessing plasma levels; therefore, these findings should be interpreted with caution.

In the studies reviewed, CBD regularly showed improved clinical outcomes in GAD, SAD, and anxiety related to PTSD, with minimal adverse effects, which differs from other therapeutic agents that are currently used for these indications. These results indicate that CBD could provide a unique therapeutic opportunity to augment or replace existing pharmacotherapy in patients with inadequate relief while causing fewer adverse effects. While CBD did show positive benefits in these patient populations, it can be challenging to translate results across studies owing to the lack of a standardized assessment tool and the variety of dosing schedules and routes of administration that were used. The most regularly used screening tool in CBD studies is VAMS, but its use has not been universal. Further standardized approaches in dosing and outcome measurement will be useful to best determine an effective therapeutic dose of CBD for broader patient populations.

Of note, the increasing amount of human studies evaluating the role of CBD in the treatment of anxiety and anxiety-related disorders are showing potential therapeutic success, specifically when CBD is administered with acute dosing. Fewer studies exist that evaluate the safety and efficacy of long-term

use of CBD in human populations. While clinical evidence supporting the use of CBD in these patient populations now exists, there continue to be considerable challenges in terms of a lack of standardized dosage and route of administration. These challenges also persist in terms of lack of standardization in product manufacturing. Typically, CBD products are labeled not by strength per dose, but by strength of product contained in the entire package. The labeling of these products can lead to confusion for patients attempting to follow a specific dosage schedule based on their clinical indication, suggesting a need for focused patient education and follow-up with patients initiating CBD therapy for a chronic indication.

While CBD has a generally mild adverse-effect profile as demonstrated through human studies, some clinical considerations do exist. Clinical data have demonstrated the potential for CBD to increase plasma levels of warfarin, and suggest that CBD products may potentiate some drug interactions via CYP450 pathways.[33] CBD has the potential to function as a potent inhibitor of CYP3A4 and CYP2D6, which may result in increased serum concentrations of medications such as macrolides, calcium channel blockers, antiretrovirals, antidepressants, antipsychotics, and opioids.[34,35] In addition, patients with decreased CYP2C19 or CYP3A4 function may be at risk for increased CBD accumulation and exposure, while patients taking a CYP3A4 inducer may see a decrease in CBD exposure.[33,35] Patients taking anticoagulants or other interacting medications should be counseled about the effects of initiating and discontinuing CBD products. See Table 2 for a list of other CBD considerations.

Another potential challenge surrounding the use of CBD in the general population concerns the persistent issues regarding product purity. Generally, CBD products sold to the public for medical use contain high levels of CBD and low levels of THC, although these levels of THC may range between 0.3% and 5% based on state law.[36] Even with the level of THC provided on product labeling, actual content of THC may be higher than what is listed on the label as found in FDA test results of products in 2015 and 2016.[37,38] For patients where the presence of THC could be problematic because of workplace drug screenings or because the legal status of cannabis products in their state is in question, these factors should be considered before recommendation of CBD products. In addition, because of the lack of product regulation for safety and purity given its status as a dietary supplement, products may also have a variable level of CBD present in them, further increasing difficulty in ensuring that patients receive a desired dose to obtain a specific therapeutic effect. One study in 2015 demonstrated a wide range of product content of CBD, with products sold as medical cannabis products being both over- and underlabeled in regard to CBD content.[39] Both regulation and increased quality assurance are needed for CBD products to be routinely recommended for use as a medical product.

Last, patient access to CBD products can vary. While all 50 states have legislation that legalizes CBD products, restrictions vary widely, and CBD products are still considered by the federal government to be in the same restricted access class as marijuana. In similar fashion to their approach to medical marijuana, the federal government generally declines to enforce restrictions on CBD use. The legal status of CBD is evolving, and clinicians should pay careful attention to the laws surrounding CBD sales and usage in their states.

Conclusion

CBD has consistently demonstrated acute reduction in anxiety-related symptoms in patients, specifically within GAD and SAD. Additionally, the use of CBD for these disorders has shown increasingly minimal adverse effects compared with existing pharmacotherapy. Further studies are needed to determine long-term safety and efficacy of CBD products and a more standardized dose-effect response. Clinicians should be mindful of challenges related to product purity, legal status of CBD based on geographic area, and the potential for drug interactions when recommending the use of CBD for anxiety.

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Use of Cannabidiol for the Treatment of Anxiety: A Short Synthesis of Pre-Clinical and Clinical Evidence

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Abstract

Anxiety disorders have the highest lifetime prevalence of any mental illness worldwide, leading to high societal costs and economic burden. Current pharmacotherapies for anxiety disorders are associated with adverse effects and low efficacy. Cannabidiol (CBD) is a constituent of the *Cannabis* plant, which has potential therapeutic properties for various indications. After the recent legalization of cannabis, CBD has drawn increased attention as a potential treatment, as the majority of existing data suggest it is safe, well tolerated, has few adverse effects, and demonstrates no potential for abuse or dependence in humans. Pre-clinical research using animal models of innate fear and anxiety-like behaviors have found anxiolytic, antistress, anticompulsive, and panicolytic-like effects of CBD. Preliminary evidence from human trials using both healthy volunteers and individuals with social anxiety disorder, suggests that CBD may have anxiolytic effects. Although these findings are promising, future research is warranted to determine the efficacy of CBD in other anxiety disorders, establish appropriate doses, and determine its long-term efficacy. The majority of pre-clinical and clinical research has been conducted using males only. Among individuals with anxiety disorders, the prevalence rates, symptomology, and treatment response differ between males and females. Thus, future research should focus on this area due to the lack of research in females and the knowledge gap on sex and gender differences in the effectiveness of CBD as a potential treatment for anxiety.

Keywords: cannabinoids; cannabis; CBD; clinical trials; mental illness

Introduction

Anxiety disorders are the most prevalent mental illnesses in the world, leading to high societal costs and economic burden.[1] Anxiety is characterized by excessive anticipation of future threats and accompanied by excessive fear, which is an emotional response to imminent threats.[2] Persistent fear and anxiety lead to maladaptive behavioral disturbances and disability. Anxiety disorders are associated with panic attacks, avoidance behavior, and diminished sense of well-being, leading to troubled relationships, increased rates of unemployment, and elevated risk of suicide.[3] Neuropsychiatric anxiety disorders include generalized anxiety disorder (GAD), social anxiety disorder (SAD; also known as social phobia), specific phobia, panic disorder, and agoraphobia.[2] Obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are no longer classified as anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders-5[2]; however, they both encompass excessive anxiety and share common symptomology with anxiety disorders.[3] These disorders tend to be chronic and persistent, lasting 6 months or more, and have high comorbidity rates with other anxiety disorders and mental illnesses.[2,4]

Currently, the main pharmacological treatments for anxiety disorders include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, tricyclics, partial 5-hydroxytryptamine 1A (5-HT1A) receptor agonists, and benzodiazepines.[5] These pharmacotherapies tend

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to have adverse effects and low efficacy (in only about 40–60% of patients),[4] with the majority of patients failing to achieve complete remission.[6] Anxiety disorders may additionally be treated using psychological approaches, including cognitive behavioral therapy, exposure therapy, and cognitive processing therapy,[4] although these therapies tend to be costly and limited to some therapeutic contexts.[7] Thus, there is a strong and urgent need to develop novel treatment approaches for anxiety disorders.

Cannabidiol (CBD) is a constituent of the *Cannabis* plant, which has potential therapeutic properties across many neuropsychiatric disorders.[8] Indeed, Epidiolex® (99% CBD; 0.1% Δ-9-tetrahydrocannabinol [THC]) has been approved in some places for the treatment of epilepsy[9] and clinical trials have established that CBD can be an effective treatment for pediatric epilepsy,[10,11] or epilepsy with a pediatric onset.[12,13] Interest in the broader therapeutic potential of CBD is exemplified by the burgeoning number of systematic reviews and meta-analyses published within the past few years that champion its use in a number of potential therapeutic indications. CBD is well tolerated and effective in studies of social anxiety during public speaking tasks,[1,14,15] demonstrates promising data from early trials in psychosis to treat schizophrenia[16,17] and in the early studies of motor and nonmotor symptoms of Parkinson's disease[18]; it has also shown some promise in colitis.[19] Reviews of the pre-clinical literature have also shown some preliminary ability to ameliorate cancer tumors, alcohol use disorder,[20] pain,[21] as well as acting as an anti-inflammatory, analgesic, antiarthritic, anti-Alzheimers, antidepressant, antidiabetic, as well as others.[22]

The primary psychoactive component of cannabis, THC, has its actions primarily at the cannabinoid type 1 (CB1) receptor.[23] By comparison, the pharmacological profile of CBD is very different from THC and it is currently not fully understood.[23] Nevertheless, it is known to have interactions with several receptors in both the central and peripheral nervous systems,[24] which are known to regulate fear and anxiety. These receptors include the serotonin 5-HT1A receptor, the CB1 and CB2 receptors, and the transient receptor potential, vanilloid type 1 receptor (TRPV1).[3,25] The acute anxiolytic effects of CBD at low and intermediate doses are thought to involve 5-HT1A activation.[8,26] Whereas TRPV1 antagonism allows for the anxiolytic effects of higher CBD doses, the anxiogenic effects of higher CBD doses involves TRPV1 agonism.[8,26] TRPV1 activity seems to be unique to CBD and a few other minor cannabinoids, as THC does not interact with this receptor channel.[27]

Another potential mechanism through which CBD produces anxiolytic effects is due to the action of the endogenous cannabinoid anandamide in the brain.[28] CBD has been shown to increase cannabinoid receptor activation indirectly by elevating endocannabinoid levels through its action on endocannabinoid metabolism.[29,30] CBD has the ability to inhibit fatty acid amide hydrolase (FAAH) enzyme, which metabolizes anandamide, consequently enhancing anandamide levels and indirectly increasing CB1 receptor activation.[29] CB1 receptor activation has been thought to mediate the ability of CBD to regulate long-term learned fear processing.[25] Endocannabinoid signaling is part of an endogenous anxiolytic neuromodulatory system, thus inhibition of FAAH activity is a potentially promising therapeutic approach for reducing anxiety-related symptoms.[30]

After the recent decriminalization and legalization of medical and recreational cannabis in certain countries and jurisdictions, cannabis use continues to increase.[31–33] CBD has drawn increased attention as a potential treatment, as the majority of existing data suggest that it is safe, well tolerated, and has few adverse effects.[34] The World Health Organization stated that across a number of controlled open-label trials, CBD is generally well tolerated with a good safety profile.[35–37] Several studies propose that CBD is nontoxic, does not induce changes in food intake or catalepsy, does not affect physiological measures, and does not alter psychomotor or psychological functions.[37] In addition, chronic use and high doses of up to 1500 mg/day are reportedly well tolerated in humans.[37]

Thus far, CBD demonstrates no potential for abuse or dependence in humans.[38] In one study, it was found that subjective ratings of "stoned" did not increase after administration of CBD to participants.[39] In other studies, CBD had no effects on visual analog scales of drug "high," "good drug effects," "street value,"[40] "liking," "take again," "bad effects" or alertness/drowsiness; CBD had slight effects on ratings of the positive effects of the drug.[41] THC alone or in combination with CBD increased ratings of "stoned,"[39] "high," "good drug effect," "liking," "strength," "good effect," "desire to take again"[42]; CBD thus had no effects on the subjective effects of THC. Although, it should be noted that in one study a high dose of vaporized CBD produced some intoxicating properties compared with placebo[43]; therefore, CBD may have psychotropic properties in some preparations.

Pre-Clinical Studies

The anxiolytic effects of CBD were initially explored in pre-clinical studies, using several animal models and behavioral tests. The elevated plus-maze (EPM) was one of the first tests used in rodents to study the anxiolytic effects of CBD. Guimarães et al.[44] used the EPM to demonstrate a full dose–response curve in rats, after acute systemic administration of CBD, which produced a "bell-shaped" dose–response curve. These findings indicated that CBD is anxiolytic at low and intermediate doses and produces anxiogenic-like effects at higher doses. This has been further confirmed in other animal models of innate fear and anxiety-like behaviors using various behavioral tests, such as the EPM, open field, light–dark test, and predator exposure.[25] Furthermore, using the EPM, CBD displays anxiolytic effects similar to diazepam in both mice and rats.[44,45] Other behavioral tests used include the Vogal test, classical conditioning, marble burying test, chronic unpredictable stress test, fear and predator exposure tests, and the social interaction test, which have demonstrated different findings, including anxiolytic, antistress, anticompulsive, and panicolytic-like effects in rodents (for recent reviews, see Blessing et al.,[3] Lee et al.,[8] and Papagianni and Stevenson[25]).

To examine the mechanism of CBD-mediated anxiolytic-like effects in animals, microinjection models have been utilized. When CBD was injected into specific brain regions associated with anxiety, including the central nucleus of the amygdala, the dorsal periaqueductal gray, and the bed nucleus of the stria terminalis, anxiolytic effects were produced.[3] Antagonism of the 5-HT1A receptor resulted in attenuation of anxiolytic effects, thereby potentially mediated some symptoms of anxiety.[26] Overall, pre-clinical evidence strongly supports the anxiolytic role of CBD; however, the majority of pre-clinical research has only been conducted using male animals, therefore, these findings need to be replicated using females.[3,8]

Clinical Studies

The anxiolytic effects of CBD observed in animals have provided insight and guided human research. The initial clinical studies examining the effects of CBD on anxiety were performed in the 1980s, when it was demonstrated that CBD could attenuate the anxiogenic and psychoactive effects of THC in healthy volunteers.[46,47] Since then, studies in healthy volunteers[14,46,48–50] and individuals with SAD[15,28] provide early evidence that CBD may have anxiolytic effects in humans. The Simulation Public Speaking Test has been used to examine the effects of CBD on anxiety in clinical studies. In both healthy volunteers and individuals diagnosed with SAD, it was found that in comparison with the placebo group, a 400 or 600 mg single dose of CBD significantly reduced subjective symptoms of anxiety and decreased cognitive impairment and speech performance discomfort.[15,28] Neuroimaging studies[28,48,49,51,52] of acute administration of CBD have demonstrated modified blood flow in specific brain structures associated with anxiety, including the amygdala, hypothalamus, hippocampus, and cingulate cortex.[53] In addition, retrospective studies have found CBD to be effective in reducing anxiety symptoms in patients with anxiety disorders and PTSD. These studies examined varying doses (e.g., 25–75 mg/day) and preparations (e.g., oral, sublingual spray) of CBD across different patient populations and in combination with other forms of pharmacological and psychotherapies,[54–56] although findings from such retrospective studies provide limited data due to small sample sizes and lack proper controls.

Three ongoing clinical trials are currently investigating the effects of CBD as a potential treatment for anxiety disorders.[57–59] Van der Flier et al.[57] are examining the effects of a weekly dose of 300 mg of CBD administered orally for 8 weeks, in individuals with phobic disorders. An ongoing phase 3 clinical trial is exploring the use of 200 mg ranging up to 800 mg of CBD administered in oil capsules, for the treatment of GAD, SAD, panic disorder, and agoraphobia.[58] Finally, an open label phase 2 clinical trial is currently examining the effects of a sublingual, 1.0 mg CBD tincture (10 mg/mL of CBD) three times a day for 4 weeks, in patients with an anxiety disorder diagnosis.[59] These studies are of great importance because the majority of studies assessing the effects of CBD on anxiety were conducted in healthy volunteers, and the clinical trials involving patients with SAD used small sample sizes, did not include placebo controls and did not establish a dose–response relationship between CBD plasma levels and anxiety symptom measurements.[60] In addition, future clinical trials are warranted to examine the effects of CBD on other anxiety disorders, including GAD, panic disorder, and phobic disorder, as well as anxiety-related conditions, such as PTSD and OCD.

Sex Differences in Anxiety and the Utility of CBD

The prevalence rates of anxiety disorders are approximately doubled in females compared with males and

there are differing symptoms between sexes.[2,61,62] After puberty, females are more prone to anxiety disorders compared with males, largely due to the involvement of sex chromosomes and hormones.[63,64] Females typically demonstrate increased symptom severity, comorbidity, and burden of illness.[65] In terms of symptomology, females more frequently report somatic discomfort, demonstrate more internalizing coping styles, rumination, and have higher rates of comorbid mood disorders.[61,66] Males are more likely to report strained relationships as a result of excessive worry, have an increased fear of social consequences, and are more likely to have comorbid alcohol and substance abuse.[61,66] However, symptomology varies between different anxiety disorders, is influenced by social and environmental factors, and is dependent on puberty, menstrual cycle phase, pregnancy, and menopause in females.[61,67] Males and females may respond differently to psychotropic medication[67–69]; thus, it is important to understand sex differences in anxiety disorders to better develop treatments for both males and females.

It has been demonstrated in animals and humans that THC has differential effects in males and females.[70] Sex differences have been observed in the pharmacokinetics,[71–74] pharmacodynamics,[75–78] subjective effects,[79–82] abuse liability,[83–86] and therapeutic potential of THC (for recent review see Cooper and Craft[70]). Thus, other agents that target the endocannabinoid system, such as CBD, might be expected to have similar sex-dependent effects. The pharmacokinetics of CBD differ between males and females[71,87]; however, there are nearly no sex comparisons of its effects, even in animals.[70] The majority of current pre-clinical studies have solely been conducted using male animals,[8] and to our knowledge no clinical studies have yet to explore sex and/or gender differences in CBD as a potential treatment for anxiety. Of the clinical studies that did include females,[14,15,46] no sex-specific analyses were performed. Therefore, due to the increasing prevalence of anxiety disorders and lack of effectiveness of current treatments, it is crucial to conduct research studies examining sex and gender differences in use of CBD as a potential treatment for anxiety disorders.

Conclusions

Overall, existing pre-clinical and clinical evidence supports a possible role for CBD as a novel treatment for anxiety disorders. The findings reviewed in this study demonstrate the potential of CBD to produce anxiolytic-like effects in pre-clinical models and the potential of CBD to induce acute anxiolytic effects when administered as a single dose in healthy volunteers and individuals with SAD. Although these findings are promising, future research is necessary to (1) determine the efficacy of CBD in other anxiety disorders aside from SAD in placebo-controlled clinical trials; (2) establish the most effective route of administration and appropriate dose of CBD to be utilized in treatment; and (3) determine the long-term safety and efficacy of CBD. There is a strong need to develop alternative and novel treatments for anxiety-related disorders, particularly focused on sex and gender differences, as prevalence rates, symptomology, and medication response differs between men and women. Owing to the lack of research in female animals and humans, and the knowledge gap on sex and gender differences in the effectiveness of CBD as a potential treatment for anxiety, future research should focus on this area.

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The authors declare that they do not have any competing interests.

Authors' Contributions

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Abbreviations Used

5-HT1A = 5-hydroxytryptamine 1A
CB1 = cannabinoid type 1
CBD = cannabidiol
EPM = elevated plus-maze
FAAH = fatty acid amide hydrolase
GAD = generalized anxiety disorder
OCD = obsessive-compulsive disorder
PTSD = post-traumatic stress disorder
SAD = social anxiety disorder
THC = Δ-9-tetrahydrocannabinol
TRPV1 = transient receptor potential, vanilloid type 1 receptor