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REVIEW

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

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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.

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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

M.W. wrote the first draft of the article. P.D.C. and B.B. provided some text and modifications.

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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

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