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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.
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## 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

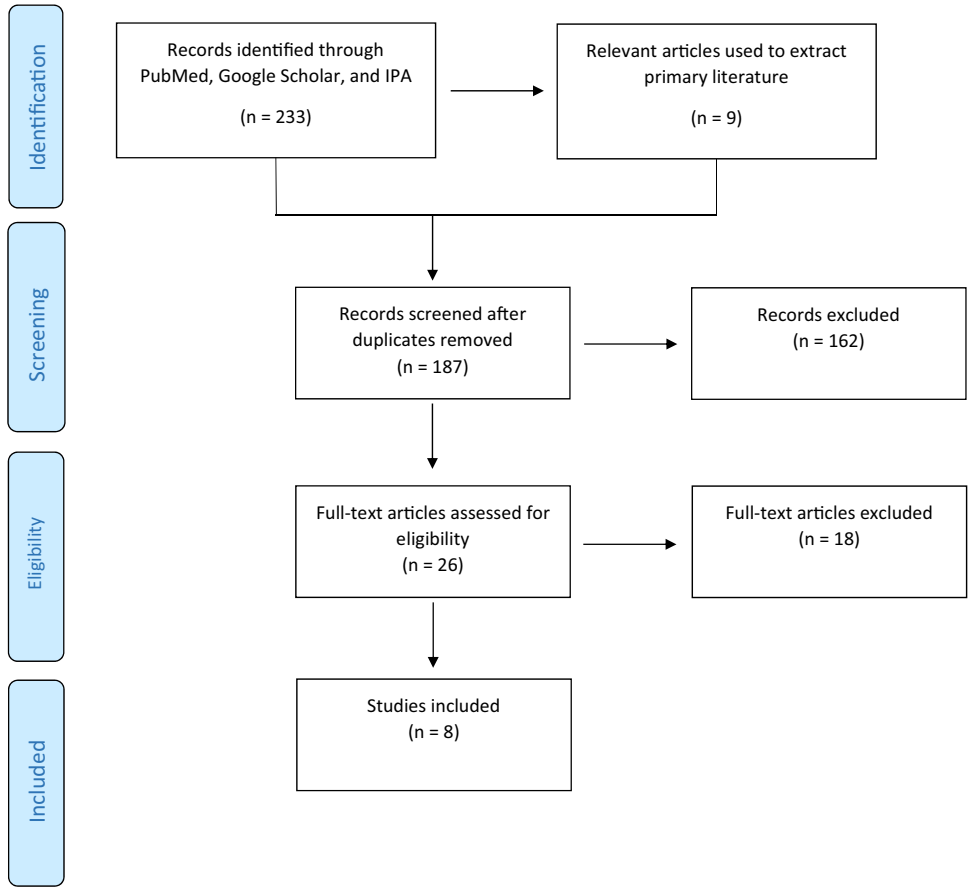


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram. Abbreviation used: IPA, International Pharmaceutical Abstracts.

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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