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A Review of Human Studies Assessing Cannabidiol's (CBD) Therapeutic Actions and Potential

The Journal of Clinical Pharmacology
2019, 59(7) 923–934
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Clinical Pharmacology
DOI: 10.1002/jcph.1387

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Abstract

Cannabidiol (CBD) is a highly touted product for many different disorders among the lay press. Numerous CBD products are available, ranging from a US Food and Drug Administration (FDA)-approved product called Epidiolex to products created for medical marijuana dispensaries and products sold in smoke shops, convenience stores, and over the Internet. The legal status of the non-FDA-approved products differs depending on the source of the CBD and the state, while the consistency and quality of the non-FDA-approved products vary markedly. Without independent laboratory verification, it is impossible to know whether the labeled CBD dosage in non-FDA-approved CBD products is correct, that the delta-9-tetrahydrocannabinol content is <0.3%, and that it is free of adulteration and contamination. On the Internet, CBD has been touted for many ailments for which it has not been studied, and in those diseases with evaluable human data, it generally has weak or very weak evidence. The control of refractory seizures is a clear exception, with strong evidence of CBD's benefit. Acute CBD dosing before anxiety-provoking events like public speaking and the chronic use of CBD in schizophrenia are promising but not proven. CBD is not risk free, with adverse events (primarily somnolence and gastrointestinal in nature) and drug interactions. CBD has been shown to increase liver function tests and needs further study to assess its impact on suicidal ideation.

Keywords

anxiety, cannabidiol, cannabis, CBD, psychosis, seizures

Cannabis sativa (marijuana) has been evaluated for the treatment of many diseases and disorders, but the altered sensory and time perception (the “high”) provided by the delta-9-tetrahydrocannabinol (delta-9-THC) component has been a barrier to wider adoption of the product by patients and medical professionals.¹ Employers may test workers or prospective workers for delta-9-THC in their hair, nails, or urine, with positive findings resulting in suspension, termination, or not being hired.¹ Finally, regulatory restrictions at the federal level and in some states make delta-9-THC-containing products illegal to possess or to transport across state lines, even for legitimate medical purposes such as seizures, nausea/vomiting, and pain/spasticity.^{2,3}

Cannabidiol (CBD) is the second most prevalent bioactive constituent of the *Cannabis sativa* plant, and unlike in some animal species, does not convert to delta-9-THC in the human body.² In vitro, animal, and human studies suggest mechanisms of action for CBD directly or tangentially related to the endocannabinoid system, as delineated in Table 1.^{2–10} There has been an incredible amount of media coverage on the health benefits of CBD, with CBD products heralded as medical breakthroughs or even miracles for all types of diseases.^{11,12}

Medical professionals may be interested in CBD as a new therapy for patients with limited traditional

options or are asked about CBD products by patients, family, and acquaintances for a host of ailments. Similarly, medical professionals might be interested in recommending CBD to patients in lieu of the medical marijuana the patient is seeking. Finally, patients may not be forthcoming about using CBD products in addition to or as a substitute for your prescribed therapy. This article provides the information medical professionals need to understand quality control issues with CBD products, CBD's pharmacokinetics and drug interaction potential, and the benefits and risks associated with using CBD for seizures, anxiety, schizophrenia, pain/spasticity, and Parkinson disease. This review will not assess the efficacy or safety of combined delta-9-THC–CBD products because the specific impact of CBD in the products cannot be determined.

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Submitted for publication 13 December 2018; accepted 16 January 2019.

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Table 1. CBD Receptor Actions and Mediated Effects^{2–10}

Receptor	Impact	Potential Pharmacologic Outcome
CBI ^a	Direct antagonism and negative allosteric modulator antagonism	Attenuation of impaired learning, memory, hypothermic, and psychosis effects induced by delta-9-THC
CB2 ^a	Antagonist + inverse agonist	Anti-inflammatory effects
GPR55	Antagonist	Anticancer effects
5HT1-alpha	Agonist	Pain relieving (allosterically regulates mu and sigma opioid receptors) and antianxiety effects
TPVR-1 ^a	Agonist	Anti-inflammatory, pain relieving, and sebum producing effects
Adenosine A2A	Enhanced adenosine concentrations	Anti-inflammatory effects

CBI, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CBD, cannabidiol; GPR55, G-coupled protein receptor; TPVR-1, 5HT1-alpha serotonin 1a receptor, transient receptor potential vanilloid receptor.

^aCBD increases anandamide concentration, an endogenous CBI, CB2, and TPVR-1 agonist.

Legality of CBD and Quality Control

In 2018, the Drug Enforcement Administration placed Epidiolex, the CBD product that was recently US Food and Drug Administration (FDA) approved for the treatment of 2 forms of drug-resistant epilepsy (Lennox-Gastaut and Dravet syndrome), in Schedule V (drugs with a relatively low risk of abuse).^{13,14} However, all other CBD products extracted from *Cannabis sativa* will remain Schedule I (high risk of abuse or harm, limited or no medicinal value, illegal to possess) until they are FDA approved and prove that, like Epidiolex, they contain less than 0.1% delta-9-THC.¹⁴ The Rohrabacher-Farr amendment, which has been in force since 2014 but needs periodical renewal in the US Congress, bars the Department of Justice from spending any funds to keep states from implementing their own laws about “the use, distribution, possession or cultivation of medical marijuana.”¹⁵ Within individual states, use of *Cannabis sativa* constituents for medicinal purposes is permissible without federal involvement as long as the states have their own laws and products are cultivated within that state and not transported across state lines.¹⁵ Clinicians should know their state’s individual laws pertaining to CBD possession and use.

The FDA-approved CBD product Epidiolex provides the concentration of CBD specified on the label with little variation over time, but this may not occur with other CBD products. In 2016, investigators purchased 84 non-FDA-approved CBD products from 31 different companies over the Internet and tested them in triplicate using high-performance liquid chromatography in a commercial laboratory.¹⁶ Triplicate test results were averaged and reported by product weight. If the average detected concentration was 90% to 110% of the labeled value, it was considered accurately labeled. With respect to CBD, only 31% (95% confidence interval [CI], 22%–41%) were labeled correctly, with 43% (95%CI, 33%–54%) of products underlabeled and 26% (95%CI, 18%–36%) overlabeled. Accuracy of labeling depended

on product type. The frequency of accurate labeling for CBD vaporization liquids, tinctures, and oils was 12.5%, 25%, and 45%, respectively. Products contained unlabeled delta-9-THC at a mean concentration of 0.45 mg/mL (range, 0–6.4) in 21% of samples.¹⁶ Inhaled doses of 2 to 3 mg and ingested doses of 5 to 20 mg of delta-9-THC can provoke adverse effects and the “high.”¹⁷ Whether there was variance within the same product from batch to batch is not known.

The FDA has issued warning letters to numerous manufacturers for false claims but also tested those products for CBD content. The FDA found that many of these products contain little to no CBD, in marked contrast to their labeled amounts.¹⁸ In the Netherlands, 8 CBD products were assessed and 4 were labeled correctly (<10% variability), 2 had 18% or 35% higher concentrations, and 2 had 74% or 98% lower CBD concentrations than the label stated, respectively.¹⁹ The delta-9-THC concentration was ≤0.03% for all CBD products.

It is impossible to know the exact dose of CBD a patient is taking if they buy products that are not FDA approved or independently tested by outside laboratories. ConsumerLabs has assessed a variety of CBD products for CBD content.²⁰ They found that the labeled CBD dosages bear little resemblance to what was contained in the products and that the cost per 10 mg of CBD ranged from \$0.80 to \$4.50. No CBD products have been verified by the United States Pharmacopeia.²¹

There are potential implications of not having an accurately labeled CBD concentration or variability in CBD concentration in products over time.²² For example, in a systematic review of non-CBD antiepileptic drugs, our University of Connecticut Evidence-Based Practice Center found that seizure control was impacted by small changes in drug concentration. While brand and generic antiepileptic drugs were equally efficacious when started de novo, switching from a brand to a

generic or vice versa increased the risk of emergency medical services or hospitalization. This suggests that using CBD products for seizure control with differing CBD content or products with variable CBD concentrations over time can be dangerous.²²

Additionally, non-FDA-approved CBD products sold in the United States could contain enough delta-9-THC to place the seller or possessor at risk of criminal prosecution under marijuana laws, even if the label does not indicate that delta-9-THC is a component of the product.¹⁶ There have been cases of people who failed drug tests for delta-9-THC claiming they used only CBD products.^{23,24}

Another risk of non-FDA-approved CBD products is adulteration and contamination. Five patients in Utah experienced symptoms such as seizures, confusion, unconsciousness, and hallucinations in 2017 due to CBD. An in-depth investigation found that a CBD product included a synthetic cannabinoid.²⁵ From that time to May 2018, a total of 52 people were harmed due to this adulterant.²⁵ Similarly, the International Cannabis and Cannabinoid Institute in the Czech Republic assessed 29 CBD products and found that 69% of them exceeded recommended levels of polycyclic aromatic hydrocarbons. Polycyclic aromatic hydrocarbons are classified as class IIa carcinogens and genotoxic mutagens according to the International Agency for Research on Cancer.^{19,26} Additionally, there is a possibility of pesticide or heavy metal contamination in unregulated CBD products.¹⁹

Pharmacokinetics/Drug Interactions

Pharmacokinetic and drug interaction data comes from the CBD prescription product Epidiolex.¹³ This form of CBD is available as a clear oral solution with 100 mg/mL in a 100-mL bottle. CBD demonstrates a less-than-dose-proportional increase in concentration over the range of 5 to 20 mg/kg/day in patients. At steady state, the time to maximal concentration is 2.5 to 5 hours, the volume of distribution is very high at 20963 to 42849 L, and the elimination half-life is long at 56 to 61 hours. High-fat/high-calorie meals dramatically increase the maximum concentration and the area under the curve (AUC) by 5- and 4-fold, respectively, but no specific recommendations are given as to whether CBD should be administered with food or on an empty stomach.¹³

Following a single CBD 1500-mg dose (1.1 times the maximum recommended daily dosage) the plasma clearance is 1111 L/h.¹³ CBD is primarily metabolized in the liver by cytochrome P450 (CYP2C19 and CYP3A) and uridine 5'-diphoglucuronosyltransferase (UGT1A7, UGT1A9, and UGT2B7).¹³

The impact of CYP3A and CYP2C19 inducers and inhibitors on CBD was explored for a combined CBD/delta-9-THC product.²⁷ Thirty-six healthy male subjects were given 4 oromucosal sprays from a product delivering 10 mg of CBD at baseline and then after therapy with the enzyme inducer rifampin (600 mg daily), the CYP3A inhibitor ketoconazole (400 mg daily), and the CYP2C19 inhibitor omeprazole (40 mg daily). The maximum concentration and AUC went down 52% and 59% with concomitant rifampin, went up 89% and 165% with concomitant ketoconazole, and was unchanged with omeprazole.²⁷

The main metabolite of CBD is the 7-OH-CBD metabolite that is subsequently converted into the 7-COOH-CBD metabolite. After repeat dosing, 7-OH-CBD and 7-COOH-CBD metabolites have an AUC that is 38% lower and 40-fold higher than CBD's AUC.¹³ According to the package insert, only the 7-OH-CBD is biologically active in preclinical seizure models, but the 7-COOH-CBD metabolite might also be an anticonvulsant.^{13,28} Protein binding of CBD and its metabolites was found to be 94% in vitro. CBD can be excreted in feces with some minor renal clearance.¹³

CBD inactivates some CYP enzymes in the short term but then, like other anticonvulsants, induces them with chronic dosing.²⁸ Upregulation of CYP3A4, CYP2C, and CYP2B10 messenger RNA have occurred in mice and induction of CYP1A1 occurred in vivo.²⁸ In contrast, CBD seems to be inhibitor of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 metabolism.¹³

To test CBD's enzyme inhibition and induction effects, the impact of Epidiolex on clobazam and its N-desmethyloclobazam metabolite were assessed in 13 subjects (age range, 4-19 years) with refractory epilepsy.²⁹ The mean increase in clobazam and N-desmethyloclobazam levels was 60% and 500%, respectively, after 4 weeks of concomitant therapy. CBD was determined to be a CYP2C19 inhibitor.²⁹ The package insert therefore suggests that clinicians consider a reduction in dosage of sensitive CYP2C19 substrates such as diazepam and clobazam, as clinically appropriate, when coadministered with CBD.¹³

A pharmacokinetic assessment of CBD was conducted in the presence or absence of the CYP3A substrate and weak inhibitor fentanyl.³⁰ Subjects ($n = 17$) were given either 400 mg or 800 mg of CBD orally with either fentanyl 0.5 μ g/kg or 1.0 μ g/kg. CBD concentrations were not significantly altered by fentanyl regardless of dose (mixed linear model $P = \text{NS}$). Unfortunately, plasma fentanyl concentrations were undetectable with either CBD 400-mg or CBD 800-mg doses, so the impact of CBD on fentanyl is not known.³⁰ As such, the impact of CBD on opioids in general is not known.

Taken together, the pharmacokinetic and drug interaction data suggest a strong risk of drug interactions with many CYP and UGT substrates (especially CYP2C19 substrates), CYP inducers, and CYP 3A inhibitors.^{13,28,29} Much more research is needed to determine how to manage patients, especially those with refractory seizures on multiple drugs impacting the CYP enzyme system. The potential for so many drug interactions makes patient use of CBD without input from a health care professional risky.

Seizure Disorders

The role of CBD in patients with epilepsy was investigated in 6 randomized trials totaling 555 subjects, 5 of 6 being double blinded and placebo controlled.³¹ In a meta-analysis of these trials in 2018, several notable pooled results were found and reported as relative risk (RR with 95%CI). CBD increased the percentage of patients with a $\geq 50\%$ reduction in seizures ($n = 2$ trials [$n = 291$]; RR, 1.74 [95%CI, 1.24–2.3]) and those achieving complete seizure freedom ($n = 3$ trials [$n = 306$]; RR, 6.17 [95%CI, 1.50–25.32]) vs placebo while increasing health-related quality of life ($n = 2$ trials [$n = 274$]; RR, 1.73 [95%CI, 1.33–2.26]). While the meta-analysts found low statistical heterogeneity ($I^2 = 0$ for all 3 comparisons), this measure is weak when there are only 2 trials being pooled. For 2 outcomes, $>50\%$ reduction in seizures and health-related quality of life, only patients with Dravet syndrome and Lennox-Gastaut syndrome were included. For complete seizure freedom, only 15 of the 306 included patients had a different seizure disorder (secondary generalized epilepsy). Furthermore, the number of patients is low, so when they attempted subgroup analyses in pediatric and adult populations, they were unable to identify significant effects for the aforementioned outcomes, but the direction and general magnitude of effects were in line with the pooled result. The strength of evidence, as determined by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, was low for each of the outcomes measures. These meta-analysts also pooled data from noncontrolled studies including open-label trials, retrospective observational studies, case reports, and surveys. Unfortunately, they did not restrict this to CBD products alone but also included products with delta-9-THC. It is impossible to tease out the sole impact of CBD, and even so, the statistical heterogeneity for the aforementioned outcomes was very high (I^2 values of 78.2%, 77.3%, and 93.9%, respectively), undercutting confidence in the results.³¹

Two of the randomized trials included in this meta-analysis greatly influenced the results and deserve special mention. They both utilized the Epidiolex version

of CBD. The first multicenter, double-blind, placebo-controlled trial included 120 children and young adults with Dravet syndrome and drug-resistant seizures.³² They were randomized to receive CBD oral solution at a dose of 20 mg/kg/day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with CBD as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference, -22.8% ; 95%CI, -41.1 to -5.4 ; $P = .01$). The percentage of patients who had at least a 50% reduction in seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95%CI, 0.93–4.30; $P = .08$). The percentage of patients who became seizure free was 5% with cannabidiol and 0% with placebo ($P = .08$). The patient's overall condition improved by at least 1 category on the 7-category Caregiver Global Impression of Change scale in 62% of the cannabidiol group as compared with 34% of the placebo group ($P = .02$).³²

In another multicenter, double-blind, placebo-controlled trial, patients ($n = 225$) with Lennox-Gastaut syndrome (age range, 2–55 years) who were resistant to other therapy with 2 or more seizures per week, were randomized to receive CBD oral solution at a dose of either 10 mg/kg of CBD twice daily (high-dose CBD), 5 mg/kg twice daily (low-dose CBD), or matching placebo for 14 weeks.³³ The median number of drop seizures at baseline was 85 seizures/28 days, and the primary end point was the change in frequency of drop seizures versus placebo. The median percent reduction from baseline in drop-seizure frequency was 41.9% in the high-dose CBD group ($P = .005$) and 37.2% in the low-dose CBD group ($P = .002$) vs 17.2% in the placebo group.³³

There were also 2 open-label studies that assessed the Epidioles form of CBD that were included in the meta-analysis and deserve special mention.³⁴ The first open-label, before-and-after study was unique in that it investigated patients with tuberous sclerosis complex–induced refractory epilepsy and explored the potentiation of clobazam's effect when used concurrently with CBD. After an initial baseline period of 1 month, the 18 patients began treatment with CBD. The initial dose of 5 mg/kg/day was increased by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day, if tolerated. CBD reduced the median weekly seizure frequency during the baseline period (22.0; interquartile range [IQR], 14.8–57.4), which decreased to 13.3 (IQR, 5.1–22.1) after 3 months of treatment with CBD. The median percent change in total weekly seizure frequency was 48.8% (IQR, 69.1%–11.1%) after 3 months of

treatment. The 50% responder rates over the course of the study were 50%, 50%, 38.9%, 50%, and 50% after 2, 3, 6, 9, and 12 months of treatment with CBD, respectively. In patients taking clobazam concurrently with CBD ($n = 12$), the responder rate after 3 months of treatment was 58.3%, compared to 33.3% in patients not taking clobazam ($n = 6$).³⁴

The second open-label trial is unique in that patients ($n = 214$; age range, 1–30 years) with refractory seizures regardless of genetic etiology were enrolled, although approximately 40% had either Dravet syndrome or Lennox-Gastaut syndrome.³⁵ Patients (age range, 1–30 years) receiving stable doses of antiepileptic drugs before study entry were enrolled in an expanded-access program at 11 epilepsy centers. Patients were given oral CBD at 2 to 5 mg/kg/day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (depending on study site). Of the 214 enrolled patients, 64% of patients had a long enough follow-up period to be included in the efficacy analysis. The median monthly frequency of motor seizures was 30.0 (IQR, 11.0–96.0) at baseline and 15.8 (5.6–57.6) over the 12-week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR, 0–64.7).³⁵

Anxiety

There are many studies assessing the impact of CBD on feelings of anxiety. Unfortunately, these studies have very small sample sizes.^{36–48} This means exaggerated responses or lack of significant effects could be due to a lack of statistical power. All of the studies use single-dose CBD, so the chronic impact of the drug cannot be determined. As such, only generalizations about using CBD prophylaxis before or after an anxiety-provoking event can be made. In all but 3 trials, study subjects were normal volunteers, so the extent of their anxiety given the prescribed stressor might be different from that seen in patients with social anxiety disorder or generalized anxiety disorder. Responses from normal volunteers to a stressor might be less severe than people with anxiety disorders, diminishing the extent of benefit that could result from effective treatment.^{36–48}

The first category of studies assessed the impact of single-dose CBD to attenuate the anxiety-promoting effects of single-dose delta-9-THC.^{36–39} These trials suggest that CBD reduces higher-dose delta-9-THC-induced anxiety as assessed by subjective ratings or the validated Visual Analog Mood Scale or State-Trait Anxiety Inventory. In all of these trials, higher-dose delta-9-THC is the stressor that precipitates anxiety that CBD is counteracting. It seems intuitive, given CBD's ability to impede CB1 agonism from delta-9-THC, that these attenuated anxiety effects would occur. This literature base should not be used as evidence of

anxiolytic effects arising from things other than delta-9-THC or synthetic cannabinoid CB1 agonism.^{36–39}

Prophylaxis with CBD a couple of hours before public speaking (the anxiety stressor) might provide relieve from anxiety during or shortly after the speech (Table 2).^{40–42} The studies comparing multiple CBD doses were likely underpowered to assess all doses adequately, but the 300-mg dose might provide greater benefits than smaller or larger doses. This U-shaped relationship between CBD dose and efficacy could suggest a single effective dose for all patients or might be misleading because the patients were generally similar in size and general health.^{40–42} In seizure disorders, a weight-based dosing strategy is employed, so the optimal dose is determined by body size, not a single dose.^{32,33} The benefits derived from CBD were not as robust as the benzodiazepine clonazepam in one study, but clonazepam did significantly induce sedation, whereas CBD did not.^{40–42} CBD should not supplant the use of β -blockers or benzodiazepines for public speaking-induced anxiety.

In subjects with or without chronic anxiety issues, the acute use of CBD before undergoing stressful or anxiety-provoking situations (aside from public speaking) was assessed in multiple trials (Table 3).^{43–48} Unfortunately, the results of the trials are inconsistent, and it is unclear whether patients taking CBD before non-public speaking anxiety-provoking events is an effective strategy. The variances in CBD doses, manufacturers, routes of administration, durations between CBD dosing and stressor, total evaluative times, anxiety rating scales, and stressors can all introduce heterogeneity, as can the small sample sizes employed.^{43–48}

Schizophrenia and Psychosis

There are 3 randomized trials assessing the impact of moderate-length CBD therapy on patients with schizophrenia.^{49–51} They all demonstrate a reduction of schizophrenia symptomatology over time for at least some measures but differ as to the impact of CBD therapy on the disease. Two of the trials are placebo controlled, and 1 had an active control. Each of the trials are relative small, compromising power for detecting significant differences between groups.^{49–51}

In a recent double-blind trial, patients with schizophrenia were randomized to receive CBD 1000 mg/day (manufacturer not specified) or placebo alongside their existing antipsychotic medication.⁴⁹ No patients received dual traditional antipsychotic therapy during the trial. Participants ($n = 88$) were assessed before and after 6 weeks of treatment. At the end of the trial, the CBD group had a greater reduction in Positive and Negative Syndrome Scale (PANSS) positive scores from baseline (-3.2 ± 2.6

Table 2. CBD Effects on Public Speaking Anxiety^{40–42}

Study Name and Subject Number	Study Design and Duration	CBD and Control Dose and Route
Public Speaking Stress Studies		
Bergamaschi 2011 (n = 24)	Subjects (n = 24) with untreated social anxiety disorder. R, DB, PC; single dose. CBD or placebo was also included for comparative purposes. Evaluations: baseline, 80 minutes after ingestion (pretest), immediately before speech (anticipatory), during speech, and 15 and 35 minutes post speech	CBD 600 mg (STI Pharmaceuticals & THC Pharmaceuticals) or placebo; oral
<i>Results:</i> CBD 600 mg significantly reduced VAMS anxiety, VAMS discomfort, and VAMS cognitive impairment during the speech vs placebo. No significant benefits on VAMS occurred vs placebo during the pretest, anticipatory phase, and 15 and 35 minutes after speech. CBD 600 mg significantly reduced SSPS-N scores vs placebo both in the anticipatory phase and during the speech but not at other time periods. <i>Conclusions:</i> Premedicating with CBD 600 mg reduced anxiety.		
Zuardi 2017 (n = 60)	Normal volunteers. R, DB, PC, AC; single dose. Evaluations: baseline, 80 minutes after ingestion (pretest), during speech, and 60 minutes after speech	CBD 100, 300, 900 mg (BSPG-Pharm), placebo or clonazepam 1 mg; oral
<i>Results:</i> VAMS anxiety significantly reduced with clonazepam during and 1 hour after the speech, and it was reduced with CBD 300 mg 1 hour after speech vs placebo. CBD 300 mg subjects had higher SBP and DBP during public speaking than with clonazepam. No other differences observed between groups at other times. <i>Conclusion:</i> Premedicating with CBD 300 mg reduced anxiety after public speaking.		
Linares 2018 (n = 57)	Normal volunteers. R, DB, PC; single dose. Evaluations: baseline, 90 minutes after ingestion (pretest), immediately before speech (anticipatory), during speech, immediately after speech, and 30 minutes after speech	CBD 150, 300, 600 mg or placebo; oral
<i>Results:</i> VAMS anxiety significantly reduced with CBD 300 mg during the speech vs placebo but not with the other 2 doses of CBD. No other VAMS anxiety differences observed between groups at other times, although all of the CBD groups were qualitatively lower than the placebo group at all evaluable time points. <i>Conclusion:</i> Premedicating with CBD 300 mg reduced anxiety during public speaking.		

AC, active controlled; DB, double blind; CBD, cannabidiol; DBP, diastolic blood pressure; PC, placebo controlled; R, randomized; SBP, systolic blood pressure; SSPS-N, Negative Self-Statement Public Speaking Scale; VAMS, Visual Analog Mood Scale.

vs -1.7 ± 2.8 ; $P = .019$). No significant differences were seen for PANSS total (-11.2 ± 7.9 vs -8.8 ± 8.9 ; $P = .133$) or PANSS general (-5.3 ± 4.3 vs -4.1 ± 4.8 ; $P = .196$) scores but were trending in a positive direction, while the PANNS negative score showed no CBD impact at all (-2.7 ± 3.6 vs -2.9 ± 3.1 ; $P = .965$). At the end of treatment, 78.6% of CBD-treated patients were rated by their clinician as “improved” on the Clinical Global Impression–Improvement scale compared to 54.6% of placebo-treated patients ($P = .018$). At baseline, the distribution of Clinical Global Impression–Severity scores in the 2 treatment arms was similar, with the majority of patients in both groups classed as moderately, markedly, or severely ill. By the end of treatment, the proportion of patients in these 3 categories had decreased from 83.4% to 54.8% in the CBD group and from 79.6% to 63.6% in the placebo group ($P = .044$). At baseline, the Brief Assessment of Cognition in Schizophrenia composite scores and Global Assessment of Functioning scores were similar in the CBD and placebo groups. There was a trend toward improvements in the Brief Assessment of Cognition in Schizophrenia composite score (treatment difference, 1.31; $P = .068$) and the physical functioning Global Assessment of Functioning score (treatment difference, 3.0; $P = .08$) in the CBD group vs the placebo group at the end of the trial.⁴⁹

In another recent 6-week double-blind trial, patients (n = 36) with chronic schizophrenia were randomized to oral CBD (600 mg/day; STI Pharmaceuticals, Newtown, Pennsylvania) or placebo.⁵⁰ All subjects completed the PANSS at baseline and biweekly for 6 weeks and the MATRICS Consensus Cognitive Battery (MCCB) at baseline and at the end of 6 weeks of treatment. There was a significant decrease in PANSS total scores over time ($P < .0001$) but no significant drug $\times$ time interaction ($P = .18$). PANNS general, positive, and negative scores similarly found time-related reductions ($P \leq .05$ for each) with no significant drug $\times$ time interaction ($P = .56$, $P = .55$, and $P = .26$, respectively). There was no main effect of time or drug on MCCB composite score. A significant drug $\times$ time effect was observed ($P = .02$) for the MCCB composite score, but in post hoc analysis only placebo-treated subjects improved over time ($P = .03$). The main difference between this trial and the one described above is that the first trial allowed only 1 antipsychotic to be used, while in this trial a sizeable portion of patients were receiving more than 1 typical or atypical antipsychotic agent and the distribution was unequal between groups (11% in CBD vs 39% in placebo; $P = .05$). Whether the manufacturer of the CBD was different is not known, but the dose was 1000 mg in the trial above but 600 mg in this trial.⁵⁰

Table 3. CBD Efficacy With Other Stressor That Can Induce Anxiety^{43–48}

Study Name and Subject Number	Study Design and Duration	CBD and Control Dose and Route
Normal Volunteer Stress Induced Anxiety Model Studies		
Crippa 2004 (n = 10)	R, DB, PC, CO; single dose. Evaluations of the VAMS made 30 minutes before drug ingestion, at the time of drug ingestion, and at 60 minutes (at the time of stressor (cannula insertion) and 75 minutes afterwards.	CBD 400 mg (THC Pharmaceuticals) or placebo; oral
<i>Results:</i> CBD 400 mg significantly reduced VAMS anxiety scores and increased VAMS mental sedation scores significantly at both 60 and 75 minutes after ingestion versus placebo. <i>Conclusions:</i> CBD provided anxiolytic and sedative properties.		
Bhattacharyya 2010 (n = 15)	R, DB, AC; single dose. Drugs taken 1 hour before fMRI scanning and scanning lasted for 1 hour. Assessments made at baseline (drug admin), 1 hour (begin scan), 2 (end scan), and 3 hours (after scan). Viewing fearful faces and visual and auditory stimulation tasks were given.	CBD 600 mg (THC Pharmaceuticals), placebo, THC 10 mg, or THC 10 mg + CBD 600 mg; oral
<i>Results:</i> CBD alone did not impact the PANNS, STAI, or VAMS scores vs placebo at any time point, but THC alone did. In a second phase, pretreatment with CBD attenuated THC induced PANNS score increases significantly at 30 minutes. <i>Conclusions:</i> CBD did not alone provide antianxiety or psychotic effects but did attenuate the psychotic effects of THC.		
Das 2013 (n = 48)	R, DB, PC; single dose. Subjects were shocked according to a room-specific pattern, and then the pattern was repeated but no shocks were given, both on the same day. CBD was given either before the second pattern occurred or after. Then subjects came back another day to repeat the procedure. The MRS was determined before and after the procedures on both days.	CBD 32 mg (STI Pharmaceuticals) or placebo; inhaled (vaporized)
<i>Results:</i> CBD and placebo both reduced the MRS anxiety score, but no significant differences occurred between them. <i>Conclusions:</i> CBD did not provide antianxiety effects to electrical shocks.		
Arndt 2017 (n = 38)	R, DB, PC, CO; single dose. Drug administered 2.5 hours before testing began. Mood evaluations conducted over 4.75 hours.	CBD 300, 600, 900 mg (Insys Therapeutics) or placebo; oral
<i>Results:</i> POMS, IAPS, DEIT, ABT, CB, ES scales showed no differences between groups. <i>Conclusion:</i> CBD did not provide antianxiety effects after emotional, anxiety-producing stimuli.		
Hundal 2018 (n = 32)	R, DB, PC; single dose. Three-dimensional virtual reality provided the stressor. Evaluations conducted 130 minutes after taking CBD or placebo. Mood evaluations conducted at baseline and immediately after leaving the virtual reality scenario. Cortisol, SBP, DBP, HR taken periodically throughout.	CBD 600 mg (GW Pharmaceuticals) or placebo; oral
<i>Results:</i> Anxiety outcomes (BAI, UMACL) and persecutory ideation outcomes (SPSS, CAPE) showed no significant differences between groups after the stressor. CBD showed trend toward increased anxiety via the BAI post-stressor ($P = .09$). No differences in cortisol, SBP, DBP, or HR between groups. <i>Conclusions:</i> CBD provided no antianxiety or persecutory ideation effects.		
Cannabis User Stress-Induced Anxiety Models		
Hindocha 2015 (n = 48)	R, DB, PC, CO; single dose. Assessments: Subjects completed an emotional facial affecter cognition task including fearful, angry, happy, sad, surprised, and disgusted varying in intensity from 20% to 100%. Baseline evaluations conducted followed by drug inhalation and retesting began 10 minutes thereafter.	CBD 16 mg (STI Pharmaceuticals), THC 8 mg or placebo; inhaled (vaporized)
<i>Results:</i> CBD and THC had no effect on VAS scores for anxiety. CBD enhanced correct facial recognition for facial images at 60% intensity but not the others while THC reduced facial recognition at 40% intensity. <i>Conclusions:</i> CBD did not provide beneficial antianxiety effects.		
Studies in Patients Diagnosed With Social Anxiety Disorder		
Crippa 2011 (n = 10)	R, DB, PC, CO; single dose. Evaluations of the VAMS made 30 minutes before drug ingestion, at the time of drug ingestion, and at 60 minutes (cannula insertion), 75 minutes (stress period), and 140 minutes (after stress).	CBD 400 mg or placebo; oral
<i>Results:</i> Subjects had severe baseline anxiety via the SPIN and BSPS scores of >52 and >54 , respectively. CBD group had lower VAMS anxiety scores at 60, 75, and 140 minutes after dosing vs placebo, but there were no differences between groups for VAMS mental or VAMS physical sedation scores vs placebo. <i>Conclusion:</i> CBD therapy reduces anxiety during a stressful event.		

ABT, Attentional Bias Task; AC, active controlled; BAI, Beck Anxiety Inventory; BSPS, Brief Social Phobia Scale; CAPE, Community Assessment of Psychic Experiences; CB, Cyberball; CBD, cannabidiol; DB, double blind; DBP, diastolic blood pressure; DEIT, Dynamic Emotion Identification Task; ES, Emotional Stroop; fMRI, functional magnetic resonance imaging; HR, heart rate; IAPS, International Affective Picture System; MRS, Mood Rating Scale; PANNS Positive and Negative Syndrome Scale; PC, placebo controlled; POMS, Profiles of Mood State; R, randomized; SBP, systolic blood pressure; SPIN, Social Phobia Inventory; SSPS, State Social Paranoia Scale; SSPS-N, Negative Self-Statement Public Speaking Scale; STAI, Spielberger State Trait Anxiety Inventory; UMACL, University of Wales Mood Adjective Checklist; VAMS, Visual Analog Mood Scale.

In the final double-blind, randomized trial, CBD (manufacturer unspecified) was directly compared to the atypical antipsychotic amisulpride in patients (n = 39) with acute schizophrenia.⁵¹ After 3 antipsychotic-free days (or >3 months after a depot injection),

patients were randomized to 200 mg of CBD or amisulpride daily, which could be increased by 200 mg/day to a daily dose of 200 mg 4 times daily (total 800 mg/day) within the first week. This dosage was maintained for another 3 weeks, although a reduction to 600 mg/day

was allowed for unwanted side effects after week 2. Three patients in the CBD group and 5 in the amisulpride group had their dose reduced to 600 mg during the maintenance phase. The usual dosage of amisulpride is 400 to 800 mg, and this antipsychotic's efficacy is in line with that provided by other antipsychotic agents, so this is a fair comparator. The PANSS and the Brief Psychiatric Rating Scale were primary outcome measures of psychotic symptoms at baseline, day 14, and day 28. The PANNS total, general, positive, and negative scores as well as the Brief Psychiatric Rating Scale scores significantly improved in both groups vs baseline at 14 and 28 days, but there were no significant differences between the 2 groups at any time point. CBD therapy, but not amisulpride therapy, significantly increased the serum concentrations of anandamide on days 14 and 28. The association between the change in anandamide concentrations and the reduction in the PANNS score was significant for CBD-treated patients ($P < .001$) but not amisulpride-treated patients ($P = .641$).⁵¹

The impact of single-dose CBD (either 300 mg or 600 mg) vs placebo was assessed in patients ($n = 28$) with schizophrenia using a double-blinded methodology.⁵² It is unclear whether it was randomized or the investigators placed subjects into the groups intentionally to balance demographic factors. This study investigated the effects of CBD on selective attention using the Stroop Color Word Test, a measure of cognition. The subjects attended 2 experimental sessions, the first without the administration of drugs or placebo. In the second session, the subjects underwent the same procedures an hour after taking their CBD or placebo. The 3 groups did not differ significantly with respect to electrodermal measures in the 2 experimental sessions. When the first and second sessions were compared, both the placebo group and the CBD 300 mg significantly improved ($P < .05$), as evidenced by fewer errors, but the CBD 600-mg group only showed a trend toward improvement ($P > .05$ but $< .10$). This suggests that people were better educated about the test, not because CBD was providing benefits in cognition.⁵²

Aside from patients with schizophrenia, there were 2 double-blind trials assessing the impact of single doses of CBD on attenuating the acute psychotic-like effects of delta-9-THC.^{44,53} Bhattacharyya⁴⁴ was the first of these trials, which not only assessed symptoms of psychosis via the PANNS score but also assessed for anxiety. Bhattacharyya found no impact of CBD versus placebo on PANNS but did find suppression of delta-9-THC-induced changes at 30 minutes (Table 3).

In a double-blind trial of people without schizophrenia, healthy participants ($n = 48$) were randomized to receive single-dose oral CBD 600 mg or placebo 210 minutes before intravenous delta-9-THC 1.5 mg.⁵³ After delta-9-THC administration, there were lower

PANNS positive scores in the CBD group, but this did not reach statistical significance. However, clinically significant positive psychotic symptoms (defined a priori as increases ≥ 3 points) were less likely in the CBD group compared with the placebo group (odds ratio, 0.22, χ^2 , 4.74; $P < .05$). Post-delta-9-THC paranoia, as rated with the State Social Paranoia Scale, was lower in the CBD group compared with the placebo group ($t = 2.28$; $P < .05$). Finally, episodic memory via the Hopkins Verbal Learning Task-Revised showed less decline with CBD than with placebo ($-0.4\% \pm 9.7\%$ vs $-10.6 \pm 18.9\%$; $P < .05$).⁵³

Pain and Spasticity

The studies assessing CBD alone for pain relief are scant, and 2 of 3 use methodologies with weak strength of evidence.^{54,55}

An open-label, single-arm study investigated the short-term effect of CBD-enriched hemp oil for relieving symptoms and improving the quality of life in young girls ($n = 12$; age range, 12-24 years) with significant somatoform psychological and chronic pain as a result of the human papillomavirus vaccine.⁵⁴ Pain issues included chronic headache, fibromyalgia, arthralgia, myalgia, and gastrointestinal pain among the girls. All of the girls were given sublingual CBD-rich hemp oil drops, 25 mg/kg/day supplemented by 2 to 5 mg/mL of CBD once a week until a maximum dose of 150 mg/mL of CBD per day was reached over a 3-month period. Two patients dropped out due to adverse events, and another 2 patients stopped the treatment early due to lack of any improvement, so only 8 of the patients (66.7%) had evaluable data. Compared to baseline, after patients received the CBD-enriched hemp oil, there were significant reductions in body pain, the physical component score, vitality, and social role functioning using the SF-36 questionnaire ($P < .05$ for each).⁵⁴

A second open-label, single-arm trial assessed for pain relief in kidney transplant patients. Patients ($n = 7$; age range, 58-75 years) with renal transplant asking for pain relief received increasing doses of oral CBD 50 to 150 mg twice a day for 3 weeks.⁵⁵ Two patients had total pain improvement, 4 had a partial response in the first 15 days, and 1 had no change. No statistical tests were applied.⁵⁵

Whether the benefits seen in these trials were due to CBD, natural alleviation of symptoms over time, or the placebo effect cannot be determined. The first trial could be confounded by a lack of intention-to-treat methodology with a high withdrawal rate.⁵⁴ Similarly, the first trial used CBD-enriched hemp oil, where constituents in the hemp oil aside from CBD might have provided some of the benefits on their own.⁵⁴

There was 1 randomized, double-blind, multigroup crossover trial assessing pain and spasticity. In this trial, patients ($n = 24$) with multiple sclerosis, spinal cord injury, brachial plexus damage, and limb amputation due to neurofibromatosis were enrolled.⁵⁶ They received CBD, delta-9-THC, CBD + delta-9-THC, or placebo for 2 weeks during each phase of the trial in a crossover fashion with their pain, spasm, spasticity, bladder function, and coordination assessed by a daily self-administered visual analogue scale (0 = worst to 100 = best) recorded over the last 7 days of each phase and averaged. The CBD group had significantly better pain control (54.8 ± 22.6 vs 44.5 ± 22.7 ; $P < .05$) but no significant improvements in spasm (54.6 ± 19.1 vs 47.3 ± 22.6), spasticity (47.8 ± 18.5 vs 42.3 ± 18.1), bladder function (60.5 ± 28.4 vs 54.9 ± 28.8), or coordination (38.3 ± 22.9 vs 40.6 ± 21.1) vs placebo. The biggest weaknesses in this trial is the incomplete data set and lack of intention-to-treat analysis with only 12 patients, 16 patients, and 8 patients completing the pain, spasm, and spasticity assessments, respectively. The grouping together of different painful and spasm-inducing disorders instead of focusing on a single one like multiple sclerosis is also a weakness of the trial given the small sample size. In an assessment using 20 of the 24 subjects, CBD reduced spasm severity (3.8 ± 2.0 vs 5.4 ± 2.3 ; $P < .05$ [score out of 10 with larger numbers meaning greater severity]) but not frequency (4.6 ± 2.2 vs 4.9 ± 2.5). The other treatment group comparisons (delta-9-THC and CBD + delta-9-THC vs placebo are not displayed in the present review.⁵⁶

Parkinson Disease

The only available trial of CBD in Parkinson disease did not find benefits in the movement aspect of the disorder but may impact sleep.^{57,58} Twenty-one patients with Parkinson disease without dementia or comorbid psychiatric conditions were assigned placebo, CBD 75 mg/day, or CBD 300 mg/day for 6 weeks.⁵⁷ The group receiving CBD 300 mg/day had significant improvements versus placebo in the Parkinson's Disease Questionnaire-39 ($P = .05$). No differences were found in or between any group for the Unified Parkinson Disease Rating Scale, concentrations of brain-derived neurotrophic factor, or in proton magnetic resonance spectroscopy indices.⁵⁷

In the trial described above, 4 subjects had Parkinson disease-associated rapid eye movement sleep behavior disorder.⁵⁸ This disorder is characterized by parasomnia characterized by the nightmares and loss of muscle atonia during rapid eye movement sleep. All of the patients were receiving CBD (75 mg/day in 1 patient and 300 mg/day in 3 patients). At baseline, patients had between 2 and 4 episodes/week, but

over the 6 weeks, 3 of the patients had no events and the other patient (receiving CBD 300 mg/day) had a reduction to 1 episode per week.⁵⁸

Adverse Events

Two of the largest trials assessing patients on CBD for adverse events were in young patients with genetically determined refractory seizures. In the randomized trial of patients with Dravet syndrome, adverse events occurred more frequently in the CBD group than in the placebo group, including somnolence (36% vs 10%), diarrhea (31% vs 10%), fatigue (20% vs 3%), vomiting (15 vs 5%), pyrexia (15% vs 8%), and lethargy (13% vs 5%).³² More patients had increased aminotransferase levels with CBD than placebo (12 vs 1), and there were more withdrawals from the trial in the CBD group (8 vs 1). The drug interaction between CBD and clobazam likely accentuated the somnolence, since 18 of the 22 CBD patients with somnolence also took clobazam.³² Similarly, in the randomized trial of patients with Lennox-Gastaut syndrome, the most common adverse events among the patients in the CBD groups were somnolence, decreased appetite, and diarrhea, with the events occurring more frequently in the higher-dose group.³³ Six patients in the high-dose CBD group and 1 patient in the low-dose CBD group discontinued therapy because of adverse events. Fourteen patients who received CBD (9%) had elevated liver aminotransferase concentrations.³³

In Epidiolex epilepsy trials, the risk of raising liver function tests was related to the CBD dose administered and to other drugs the patient was receiving.¹³ Alanine transaminase (ALT) elevations >3 times the upper limit of normal were reported in 17% of patients taking CBD 20 mg/kg/day compared with 1% in patients taking CBD 10 mg/kg/day. The majority of ALT elevations occurred in patients taking valproate and clobazam or valproate alone. In CBD-treated patients, the incidence of ALT elevations >3 times the upper limit of normal was 30% in patients taking valproate + clobazam, 21% in patients taking valproate, 4% in patients taking clobazam, and 3% in patients taking neither drug. Clinicians should consider discontinuation or dose adjustment of valproate or clobazam if liver enzyme elevations occur. It is unclear if a pharmacokinetic drug interaction is contributing to this risk or whether it is purely pharmacodynamic. Whether the use of other drugs that can damage the liver with CBD could also accentuate the risk is unknown.¹³

Because CBD is an effective anticonvulsant therapy, the FDA is concerned that it might similarly cause suicidal ideation.¹³ There is not enough long-term data or large enough study populations to fully assess for suicidal ideation or suicides.¹³ No suicide or suicidal

ideation have yet been reported in the literature or divulged by the FDA.

The effects of CBD on hemodynamics were assessed in 2 studies. In a pharmacokinetic study evaluating CBD 400 mg or 800 mg in the presence of 2 doses of fentanyl, respiratory and cardiovascular surrogate end points (temperature, heart rate, respiratory rate, blood pressure, oxygen saturation) were determined continuously over time.³⁰ There were no occurrences of respiratory depression (breaths/min <12) or cardiovascular compromise (mean arterial pressure <60 mm Hg, heart rate >100) in any subject at any time point. CBD dose (0 mg vs 400 mg vs 800 mg) was not associated with any significant differences in vital sign parameters throughout the study (mean AUC analysis of variance, $P = \text{NS}$ for all). The higher fentanyl dose (1.0 vs 0.5 $\mu\text{g/kg}$) was associated with slightly lower respiratory rate and temperature (mean AUC $P < .05$); however, cardiovascular parameters were similar between sessions ($P = \text{NS}$).³⁰

In a single-dose crossover trial in normal volunteers, CBD had no effect on mean arterial pressure regardless of dose ($P > .05$).⁴⁶ CBD (300 and 600 mg) did not affect heart rate, but the highest dose of CBD (900 mg) resulted in a slight increase in heart rate at the last time point of the session, indicated by a significant drug $\times$ time interaction effect ($P = .036$).⁴⁶

In the direct comparative trial between CBD and amisulpride, CBD-treated patients with schizophrenia had fewer extrapyramidal symptoms and approximately 3 kg less weight gain at 28 days of therapy and less prolactin release at both 14 and 28 days than amisulpride-treated patients.⁵¹ This improved safety profile could be an important advantage for CBD either as monotherapy or as an adjunctive therapy if it provides reasonable efficacy.⁵¹

Conclusions

If patients use non-FDA-approved forms of CBD, they run the risk of variable CBD and delta-9-THC dosages, adulteration, and contamination. If not FDA approved, using a product tested by an independent laboratory is highly recommended. CBD is an effective new option for the adjunctive treatment of refractory seizures in Dravet syndrome and Lennox-Gastaut syndrome and holds promise in the treatment of other refractory seizures, but more data are needed to determine its role. Additionally, CBD is promising but not proven for premedicating before anxiety-inducing events such as public speaking and the chronic treatment of patients with schizophrenia. CBD has not been assessed for the chronic treatment of anxiety. Data in pain, spasticity, and Parkinson disease is limited and weak. CBD is not risk free, as it has both drug

interaction and adverse event potential. Somnolence and fatigue coupled with gastrointestinal disturbances are not uncommon, and rarer but serious events such as elevated liver function tests has been observed. The impact of CBD on suicidal ideation needs to be explored, as this is a serious but rare adverse event associated with other anticonvulsant drugs. Longer-term safety data are critically needed to appreciate CBD's balance of benefit to harm.

Declaration of Conflicting Interests

The author declares no conflict of interest.

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