REVIEW ARTICLE

The Role of Cannabidiol in Neurological Disorders

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Perm J 2021;25:20.156

E-pub: 02/24/2021

https://doi.org/10.7812/TPP/20.156

ABSTRACT

Cannabis has been used for both recreational and medicinal purposes for more than 4 millennia. Cannabis has been studied in various medical disorders including neurological disorders. There are well-known risks of long-term use of cannabis, including low motivation, lowered cognitive capabilities, and diminished IQ and brain mass. Cannabinoids are compounds in cannabis that are known to have therapeutic potential. The most abundant chemicals in cannabinoids are delta-9-tetrahydrocannabinol and cannabidiol. Delta-9-tetrahydrocannabinol has psychotropic effects that limits its use as a pharmacotherapeutic agent. Cannabidiol is a nonpsychotropic chemical and therefore has become a compound of interest for clinical researchers to study its therapeutic potential. This article reviews the efficacy and safety of cannabidiol in various neurological disorders in humans.

INTRODUCTION

Cannabis has been used for both recreational and medicinal purposes for more than 4 millennia.[1,2] Cannabis is made up of more than 100 compounds called cannabinoids, the most abundant chemicals of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The discovery of THC and CBD led to the identification of the cannabinoid receptors. The evidence that THC was interacting with a specific mammalian target was uncovered in murine neuroblastoma cells that expressed upregulated adenylate cyclase in response to exposure to THC or its synthetic analogues. This finding led the way for the isolation and cloning of a G protein-coupled receptor that subsequently was named cannabinoid receptor type 1 (CB1).[3] Later, cannabinoid receptor type 2 was isolated from human leukemia cells.[4] The identification of these receptors led to the hypothesis that an endocannabinoid system may exist in the mammalian body. The first endogenous cannabinoid ligand was isolated from pig brain and was named N-arachidonoylethanolamide, or anandamide.[5] The second endogenous ligand, which was named 2-arachidonoylglycerol, was isolated from intestinal tissue.[6,7] Both these ligands are arachidonic acid derivatives produced from phospholipid precursors through activity-dependent activation of specific phospholipase enzymes.[8] Several other endogenous ligands, including N-arachidonoyldopamine, N-arachidonoylglycerolether, and O-arachidonoylethanolamine were identified later on.[9]

Endogenous ligands for CB1 and cannabinoid receptor type 2 receptors in humans were named endocannabinoids.[10] CB1 receptors are found primarily in the brain and peripheral nervous system.[11] CB1 receptors in the brain are particularly concentrated in anatomic regions associated with anxiety, cognition, endocrine function, memory, motor coordination, pain sensory perception, and reward.[12,13] Cannabinoid receptor type 2 receptors, which are mainly found in immune and hematopoietic cells,[14] may be playing a role in the immune-suppressive actions of cannabinoids.[14] Endocannabinoids are therefore potential therapeutic targets for various pathological conditions, particularly neurological disorders.[15]

There are well-known risks of long-term use of cannabis, including low motivation, lowered cognitive capabilities, and diminished IQ and brain mass. THC can cause psychotropic effects, including red eyes, poor muscle coordination, delayed reaction time, increased appetite, and sudden mood changes. Therefore, its therapeutic potentials are limited. CBD does not have any psychotropic properties.[16]

Cannabis and cannabinoids have been shown to have a positive impact on a variety of neurological disorders in humans, including neuropathic pain,[17-19] migraine,[20,21] multiple sclerosis,[22] Parkinson's disease,[23,24] Huntington's disease,[25] and motor neuron disease.[26]

This review article discusses the safety and efficacy of highly purified CBD and CBD-enriched cannabis (CBD:THC ratio of 20:1). Extensive literature search on PubMed and other scientific internet platforms was done to prepare this article.

PHARMACOLOGY AND THERAPEUTIC ASPECTS IN HUMAN

Epilepsy

Both animal and human studies have proved the anticonvulsant properties of CBD.[27-29] Several studies have been conducted recently using CBD as an adjunctive therapy to assess its safety and efficacy in patients with both focal epilepsy and generalized epilepsy.[30-33]

A study in 2018 evaluated the efficacy of CBD-enriched cannabis oil extract (CBD:THC ratio of 20:1) for the treatment of drug-resistant epilepsy. Fifty-seven patients (age, 1–20 years) with drug-resistant epilepsy of various etiologies were treated with CBD-enriched cannabis oil

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Keywords: cannabidiol, cannabinoids, cannabis, CBD, delta-9-tetrahydrocannabinol, THC

Table 1. Long-term efficacy and safety of cannabidiol in patients with drug-resistant epilepsy

Disease/syndrome	Mean age (y)	Median duration (mo)	Mean dose (mg/kg/d)	Efficacy[a] (%)	Common adverse events
Seizures associated with various etiologies (57 patients)[30]	9.6 (1–20)	18	11[b]	56	Somnolence, aggression, loss of appetite
Seizures associated with Dravet syndrome, Lennox Gastaut syndrome, tuberous sclerosis complex, and others (607 patients)[35]	13 (0.4–62)	24	25[c]	52	Diarrhea, somnolence
Seizures associated with tuberous sclerosis complex (199 patients)[36]	13 (1–57)	8.9	27[c]	61	Diarrhea, seizure, loss of appetite
Seizure associated with mostly genetic epilepsies (26 patients)[37]	9 (1–17)	36	25[c]	26.9	Loss of appetite, diarrhea, weight loss

[a]Efficacy, ≥ 50% reduction.
[b]Cannabidiol:delta-9-tetrahydrocannabinol, 20:1.
[c]Highly purified cannabidiol.

extract for at least 3 months, with median follow-up of 18 months. Forty-six patients were included in the efficacy analysis. Average CBD dose was 11.4 mg/kg/day. Twenty-six patients (56%) had ≥ 50% reduction in mean monthly seizure frequency. There was no statistically significant difference in response rate among various epilepsy etiologies and cannabis strain used. Younger age at treatment onset (< 10 years) and higher CBD dose (> 11 mg/kg/day) were associated with a better treatment response. Adverse reactions were reported in 28 patients (46%) and were the main reason for treatment cessation. The common adverse events (AEs) were somnolence (14%), aggression (9%), loss of appetite (9%), and vomiting (9%). The results suggest that adding CBD-enriched cannabis oil extract to the treatment regimen of patients with drug-resistant epilepsy may result in a significant reduction in seizure frequency.[30]

GW Pharmaceutical/Greenwich Biosciences conducted randomized, double-blind, placebo-controlled studies to evaluate the efficacy of highly purified CBD oral solution add-on therapy in Dravet syndrome and Lennox-Gastaut syndrome that showed that it was efficacious for seizures associated with both these syndromes.[31-33] On June 25, 2018, the US Food and Drug Administration approved Epidiolex, a highly purified CBD oral solution, for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older.[34] This led to a long-term, expanded-access safety and efficacy study of highly purified CBD oral solution in children and adults with drug-resistant epilepsies (Table 1).[35-37] That study enrolled 607 patients with drug-resistant epilepsies from 25 US-based sites and included patients with Lennox-Gastaut syndrome, Dravet syndrome, tuberous sclerosis complex, Aicardi syndrome, CDKL5 deficiency disorder, Doose syndrome, and others. Mean age was 13 years (range, 0.4–62). Patients received highly purified CBD oral solution starting at 2 to 10 mg/kg/day, titrated to a maximum dose of 25 to 50 mg/kg/day. A total of 146 patients (24%) withdrew; the most common reasons being lack of efficacy in 89 (15%) and AEs in 32 (5%). The most common AEs were diarrhea (29%) and somnolence (22%). The median number of concomitant antiepileptic drugs was 3 (range, 0–10), the median dose was 25 mg/kg/day, and the median treatment duration was 48 weeks. Add-on highly purified CBD oral solution reduced the median monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks, and reductions were similar through 96 weeks. The proportion of patients with ≥ 50%, ≥ 75%, and 100% reductions in convulsive seizures were 52%, 31%, and 11%, respectively, at 12 weeks, with similar rates through 96 weeks. The retention rate of 76% reflects maintenance of long-term efficacy, generally mild AEs, and improvements in quality of life with CBD.[35]

Long-term safety and efficacy of highly purified CBD as an adjunctive treatment of seizures in patients with tuberous sclerosis complex was evaluated in an open-label extension trial study. A total of 199 patients participated, with a mean age of 13 years (range, 1–57 years). The study period was 267 days (range, 18–910 days). Thirty-nine patients (20%) withdrew. The mean CBD dose was 27 mg/kg/day. AE incidence was 93%, with a serious AE incidence of 15%, with 6% discontinuing CBD because of AEs. The most common AEs (≥ 20%) were diarrhea (42%), seizure (22%), and decreased appetite (20%). Elevated alanine aminotransferase/aspartate aminotransferase levels were reported in 17 (8.5%) patients. Median percentage reductions in seizure frequency (12-week windows over 48 weeks) were 54% to 68%. Seizure responder rates (≥ 50%, ≥ 75%, and 100% reduction) ranging from 53% to 61%, 29% to 45%, and 6% to 11%, respectively, across 12- week visit windows were observed. Improvement in the subject/caregiver global impression of change was reported by 87% of patients/caregivers at week 26, with 53% reporting much/very much improvement. It was concluded that long-term adjunctive CBD treatment was well

tolerated in patients with tuberous sclerosis complex, with an AE profile similar to that observed previously. Reductions in seizures were maintained through 48 weeks, with a high proportion of patients reporting global improvement.[36] On June 31, 2020, the US Food and Drug Administration approved Epidiolex (highly purified CBD) oral solution for treatment of seizures associated with tuberous sclerosis complex in patients 1 year of age and older.

Another study assessed the long-term safety, tolerability, and efficacy of highly purified CBD oral solution in children with drug-resistant epilepsy. Highly purified CBD oral solution was administered in addition to other antiepileptic treatments in 26 patients, with a starting dose of 5 mg/kg/day and weekly increment increases of 5 mg/kg/day up to a maximum dose of 25 mg/kg/day. The mean age was 9 years (range, 1–17 years). The duration of therapy ranged from 4 to 53 months (mean, 21 months). The frequency of seizures and AEs was monitored during the study period. Fifteen of 26 patients discontinued treatment, 2 patients because of serious AEs, and 13 patients because of lack of efficacy. Eleven patients completed the study. A reduction in the frequency of seizures of > 50% was noted in 38.4% of patients after 3 months of treatment, in 56.7% after 6 months, in 42.3% after 9 months, in 38.4% after 12 months, in 42.3% after 18 months, and in 34.6% after 24 months. The responder rates subsequently declined to 26.9% by 36 months and remained stable through the last follow-up (48 months), including 3 patients (11.5%) who remained seizure free. Of 26 patients, 21 (80.8%) reported AEs, among which the most frequent were reduced appetite (n = 10), diarrhea (n = 9), weight loss (n = 9), status epilepticus (n = 3), catatonia (n = 2), and hypoalbuminemia (n = 1). The limitation of this study was that the subject dropout rate after a few months into the study was high, the number of patients exposed to highly purified CBD for a long time was low, and therefore the rate of AEs over time may have been underestimated.[37]

Because the use of highly purified CBD oral solution for the treatment of drug-resistant epilepsies is increasing, a recent study monitored drug interaction between CBD and other antiepileptic drugs. CBD significantly raised serum levels of desmethylclobazam (active metabolite of clobazam), (p = <0.001), eslicarbazepine (p = 0.039), rufinamide (p = 0.004), topiramate (p = <0.001), and zonisamide (p = 0.017). CBD had no significant interaction with lacosamide, levetiracetam, perampanel, and valproate. Alanine aminotransferase/aspartate aminotransferase levels were significantly greater in participants taking concomitant valproate.[38] Another study showed an interaction between CBD and brivaracetam, resulting in an increasing level of brivaracetam.[39] One possible mechanism contributing to the increasing drug level is the inhibition of the cytochrome P450 system by CBD.

A recent study conducted a systemic chart review of pediatric patients who started highly purified CBD from January to August 2019. Among 87 patients, 9 (10%) developed thrombocytopenia. All patients who developed thrombocytopenia were taking valproic acid. No children on highly purified CBD without valproic acid (0 of 57) developed thrombocytopenia ($P < 0.0001$).[40] Another recent study evaluated food effects on the pharmacokinetics of purified CBD oral capsules in adult patients with drug-resistant epilepsy. A moderate dose of purified CBD administered with a fatty meal resulted in a 4-fold increase in C_{max} and a 14-fold increase in $AUC_{0-\infty}$. A steady-state concentration from a 300-mg dose of purified CBD, on average, was 21.3 μg/mL. The authors concluded that the fat content of a meal can lead to significant increases in C_{max} and $AUC_{0-\infty}$, and can account for variability and overall drug exposure within patients. Therefore, patients should be advised to take CBD with balanced meals to minimize fluctuations resulting from food effects.[41]

In conclusion. highly purified CBD oral solution is well tolerated even at high doses and is another promising drug as an add-on therapy in the treatment of drug-resistant epilepsy.

The overall limitation of the treatment of epilepsy with CBD may be that the number of patients exposed to long-term CBD is still low and the rate of AEs over a long period of time is not known. In addition, there is no standardization in the dose and purity of non-Food and Drug Administration-approved CBD.

Parkinson's Disease

Limited studies suggest that CBD may be used in the treatment of Parkinson's disease. An open-label pilot study evaluated the efficacy, tolerability, and safety of CBD in patients with Parkinson's disease with psychotic symptoms for at least 3 months. Six patients (4 men and 2 women) received CBD tablets (approximately 99.9% pure) in a flexible dose, starting with an oral dose of 150 mg/day for 4 weeks, in addition to their usual therapy. The patients were assessed by the Brief Psychiatric Rating Scale, the Parkinson Psychosis Questionnaire, and the Unified Parkinson's Disease Rating Scale (UPDRS). The psychotic symptoms evaluated by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire showed a significant decrease with CBD treatment. CBD did not worsen motor function and it decreased the total UPDRS scores. No AEs were observed during the treatment.[42]

In another study, CBD was studied in an exploratory double-blind trial in 21 patients with Parkinson's disease without dementia or comorbid psychiatric conditions. CBD was provided in powdered form (purity, 99%) and was placed in gelatin capsules containing either 75 mg or

300 mg. Participants were assigned to 3 groups of 7 subjects each who were treated with placebo, CBD 75 mg/day, or CBD 300 mg/day. One week before the trial and during the last week of treatment, participants were assessed with respect to 1) motor and general symptoms or UPDRS score, 2) well-being and quality of life (Parkinson's Disease Questionnaire-39), and 3) possible neuroprotective effects (brain-derived neurotrophic factor and proton magnetic resonance spectroscopy). There were no statistically significant differences in UPDRS scores, plasma BDNF levels, or proton magnetic resonance spectroscopic measures. However, the groups treated with placebo and CBD 300 mg/day had significantly different mean total scores on the Parkinson's Disease Questionnaire-39 ($P = 0.05$). The findings point to a possible effect of CBD in improving quality-of-life measures in patients with Parkinson's disease.[43] However, it is not conclusive whether CBD is effective in the treatment of neurological symptoms of Parkinson's disease because the number of patients enrolled in the studies was too small. More clinical trials with larger patient populations are needed to assess the efficacy and safety of CBD in Parkinson's disease.

Huntington's Disease

Very few human clinical trials have investigated CBD in Huntington's disease. A study assessed the symptomatic efficacy and safety of CBD for Huntington's disease. Fifteen patients were evaluated in the baseline–placebo–washout–CBD posttreatment order, and 6 patients were evaluated in the baseline–CBD–washout–placebo posttreatment order. The total daily dose of CBD (10 mg/kg) was divided into 4 capsules, and patients took 2 capsules twice a day. The patients were evaluated weekly for 15 consecutive weeks. The outcomes of the efficacy were measured by the Marsden and Quinn chorea severity evaluation scale, the Shoulson and Fahn functional disability scale for Huntington's disease, and 10 other variables. Safety was measured by a cannabis side effect inventory. The major therapeutic response variable was chorea severity as measured by the Marsden and Quinn chorea severity evaluation scale, which showed a small, nonsignificant ($P = 0.71$) response. The effects of CBD and placebo treatments on the Shoulson and Fahn disability score and 10 other variables also yielded no significant differences (all P values were > 0.05). The major safety response variables measured by the clinical laboratory tests and the cannabis side effect inventory also showed no significant difference ($P = 0.98$; Mann–Whitney test).[44]

The limitation of this clinical trial study was the small number of patients. No further clinical trials to assess the efficacy and safety of Huntington's disease have been published since.

Autism Spectrum Disorder

A retrospective study assessed tolerability and efficacy of CBD-enriched cannabis in 60 children with autism spectrum disorder and severe behavioral problems (age, 11.8 ± 3.5 years; range, 5.0–17.5 years; 77% low functioning; 83% boys). These children were treated with an oral preparation of CBD and THC at a ratio of 20:1. The dose was the dose was titrated up to effect (maximal CBD dose, 10 mg/kg/day). After the cannabis treatment, behavioral outbursts were much improved or very much improved in 61% of patients, according to the Caregiver Global Impression of Change. anxiety and communication problems were much or very much improved in 39% and 47% of patients, respectively. Disruptive behaviors improved by 29% from 4.74 ± 1.82, as recorded at baseline on the Home Situations Questionnaire–Autism Spectrum Disorder, to 3.36 ± 1.56 after CBD treatment. Parents reported less stress as reflected in Autism Parenting Stress Index scores, changing by 33%, from 2.04 ± 0.77 to 1.37 ± 0.59. AEs included sleep disturbances (14%), irritability (9%), and loss of appetite (9%). This study supports the feasibility of CBD and THC therapy in a ratio of 20:1 as a promising treatment option for refractory behavioral problems in children with autism spectrum disorder.[45]

Complex Motor Disorders

CBD was studied in children with complex motor disorders. Twenty-five children were enrolled and divided into 2 groups. Participants received a CBD:THC formulation at 20:1 or 6:1. Both groups showed improvement on the Cerebral Palsy Child Questionnaire for quality of life at the end of 5 months. They also showed significant improvement with regard to spasticity and dystonia, sleep difficulties, and pain severity. Additional research studies with randomized, controlled trials are needed to assess more comprehensively the efficacy of CBD in children with complex motor disorders.[46]

Currently there are no human studies that have investigated the effects of highly purified CBD or CBD-enriched cannabis in neuropathic pain, migraine, multiple sclerosis, motor neuron disease, and Alzheimer's disease.

CONCLUSION

In conclusion, studies on cannabis and cannabinoid compounds have shown benefits in a variety of neurological disorders in humans, but the therapeutic potentials were limited because of the psychotropic effect of THC and the long-term potential AEs of cannabinoid compounds. CBD has been found to be a promising compound that appears to be safe and efficacious. A highly purified CBD oral solution has shown efficacy and safety in Dravet syndrome, Lennox Gastaut syndrome, tuberous sclerosis complex, and other drug-resistant epilepsies. However, the clinical trials with highly purified CBD and CBD-enriched cannabis in other

neurological disorders are few and inconclusive because of low participating patient populations. Research in the future should involve larger populations and greater doses of CBD. More studies are still needed to understand the full potential and long-term effects of CBD. ❖

Acknowledgments

The author thanks Suresh Gurbani, MD, PhD, for his assistance.

Disclosure Statement

The author has no targeted funding reported.

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