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Review Article

Cannabidiol: A Review of Clinical Efficacy and Safety in Epilepsy

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ABSTRACT

Several new antiepileptic medicines became available for clinical use in the last two decades. However, the prognosis of epilepsy remains unchanged, with approximately one-third of patients continuing to have drug-resistant seizures. Because many of these patients are not candidates for curative epilepsy surgery, there is a need for new seizure medicines with better efficacy and safety profile. Recently, social media and public pressure sparked a renewed interest in cannabinoids, which had been used for epilepsy since ancient times. However, physicians have significant difficulty prescribing cannabinoids freely because of the paucity of sound scientific studies. Among the two most common cannabinoids, cannabidiol has better antiepileptic potential than tetrahydrocannabinol. The exact antiepileptic mechanism of cannabidiol is currently not known, but it modulates a number of endogenous systems and may have a novel anticonvulsant effect. However, it has broad drug-drug interactions with several agents, including inducer and inhibitor of CYP3A4 or CYP2C19. Cannabidiol can cause liver enzyme elevation, especially when co-administered with valproate. The US Food and Drug Administration (FDA) has approved pharmaceutical-grade cannabidiol oil for two childhood-onset catastrophic epilepsies: Dravet syndrome and Lennox-Gastaut syndrome. The Drug Enforcement Agency also reclassified this product as a schedule V agent. However, other cannabidiol products remain as a schedule I substance and are primarily used without regulation. Additionally, the FDA-approved pharmaceutical-grade cannabidiol oil is expensive, and insurance companies might approve this only for the designated indications. In despair, many individuals may resort to unregulated medical cannabis products in an attempt to control seizures. Rather than spontaneous treatment without medical supervision, adequate medical oversight is indicated to monitor and manage the proper dose, side effects, validity of the product, and drug-drug interactions.

Introduction

Several novel antiepileptic medicines with better safety profiles have been approved in the last two decades. Nevertheless, about a third of patients with epilepsy continue to have drug-resistant seizures, causing an increased risk of injuries, premature death, psychosocial dysfunction, and reduced quality of life.[1] Moreover, the treatment of drug-resistant epilepsy constitutes a significant health care expense, which in the United States alone approaches four billion dollars per year.[2] Many individuals with drug-resistant epilepsy are not ideal candidates for epilepsy surgery. This situation leads to patients with drug-resistant epilepsy to seek new treatments for seizures, including natural agents such as medical cannabis.

Medical cannabis is a frequent topic of discussion among the general public, patients, and physicians. With expanding popular interest, research on the use of medical cannabis for epilepsy has increased substantially in the last five years. However, there is uncertainty about several ambiguous terms related to medical cannabis. Important cannabis-related terms are summarized in Table 1.

Different marijuana strains contain varying amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a psychoactive agent, a drug of abuse, with equivocal value for seizure control and a potential to trigger seizure activity. CBD is a non-psychoactive agent, and both anecdotal and scientific evidence suggests its usefulness as an antiepileptic medication, especially for some specific epilepsy syndromes. In preclinical studies, CBD was useful in a variety of seizure models.[4-11]

In the following paragraphs, we review the legal status of cannabis, clinical pharmacology, clinical studies on epilepsy, and future directions related to the use of medical cannabis.

Conflicts of interest: None reported.

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Table 1
Terms Related to Cannabis

Cannabis	A genus of flowering plant with several recognized species such as *sativa* and *indica*. This plant is widely distributed and perhaps one of the oldest plants cultivated for human use. Its use had been described in Chinese pharmacopeias even around BCE 2700 for a number of medicinal indications by Emperor Shen Nung.[3]
Marijuana	A dried mixture of cannabis leaves and flowers
Medical marijuana	Use of cannabis or cannabis product for medical purpose
Hemp	The hearty fibers in the stalk and stems of the plant *Cannabis sativa* L. It contains minimal amounts of THC and low levels of CBD
Hemp oil	Obtained from the seeds of the hemp plant and contains a negligible amount of cannabinoids.
CBD oil	Obtained from the flowering portion of the hemp plant and doesn't contain THC
Cannabis oil	It contains concentrated cannabis extract and may have a high THC concentration
Cannabinoids	Molecules that interact with cannabinoid receptors. There are over 100 naturally occurring chemicals or phytocannabinoids including THC and CBD. Endocannabinoids are produced in the body and target the receptors. Synthetic cannabinoids are produced in the laboratory and mimic the phyto- or endocannabinoids.

Abbreviations:
CBD = Cannabidiol
THC = Tetrahydrocannabinol

Legality for medical purposes

Cannabis preparations were included as medicinal compounds in the United States Pharmacopeia from 1851 and were thought to be useful for various ailments. However, it was removed from United States Pharmacopeia in 1941 after the passage of the Marijuana Tax Act of 1937.[12] Owing to its increasing recreational use, it was classified as a schedule 1 substance (i.e. no accepted medical use and a high potential for abuse) in 1970. In tandem, the introduction of additional antiepileptic medicines prompted a gradual decrease in cannabis use for epilepsy until the recent resurgence.

Cannabis is included in Schedule IV of the United Nations' Single Convention on Narcotic Drugs, which allows individual nations to use it for medical and scientific purposes with the adoption of a licensing system for all cultivators, manufacturers, and distributors.[13] Many states in the United States have passed medical marijuana legislation to allow the sale and use of cannabis-derived products for medical therapy in epilepsy and several other medical and psychiatric disorders.[14] Regardless of these state laws, all cannabinoid components and products derived from cannabis or specifically *Cannabis sativa* (except pharmaceutical-grade CBD oil) are still considered to be controlled substances and classified as schedule I agents by the United States government and the Drug Enforcement Agency.[15] Several countries, including Australia, Canada, Germany, and the United Kingdom, have legalized the medical use of cannabis, and in some countries it can be obtained without a prescription. However, in countries such as India and Israel, it remains illegal at the federal level.[16]

Mechanism of action

Cannabinoid receptors are highly prevalent in the human nervous system, and two receptor types (CB1 and CB2) have been discovered.[17] THC has a well-documented mechanism of action via cannabinoid receptors. However, CBD has a relatively small affinity to bind CB1 and CB2 receptors and may inhibit THC binding at CB1 receptors.[18] CBD is a structurally novel antiepileptic drug and binds other noncannabinoid receptors. Several antiepileptic mechanisms to reduce neuronal excitability and neuronal transmission have been postulated such as γ-aminobutyric acid-mediated inhibition; modulation of intracellular calcium by various transient receptor potential (TRP) channels such as TRPM8, TRPA1, TRPV1, and TRPV2; orphan G-protein-coupled receptor GPR55; or voltage-dependent anion channel 1. The antiseizure effect due to anti-inflammatory action of CBD was also postulated by modulation of TNFα release or inhibition of adenosine reuptake.[19] However, further investigations are needed to find evidence of interaction between these targets and CBD and to confirm the mechanism of the anticonvulsant effects. Rather than one particular pathway, the cumulative impact of several anticonvulsant mechanisms may be responsible.

Pharmacokinetics

CBD is highly lipophilic and has poor oral bioavailability. The absorption rate of CBD is variable, and it undergoes extensive hepatic first-pass metabolism by isozymes CYP2C19 and CYP3A4.[20,21] After hydroxylation, CBD converts to 7-hydroxy CBD, which undergoes further hepatic metabolism and predominant excretion via stools.[22] CBD has a long elimination half-life, and in one study repeated daily administration of 10 mg/kg/day elicited half-life ranging from two to five days.[23] CBD rapidly distributes to highly perfused organs including the brain with subsequent equilibration to other tissues, owing to its high lipophilicity. CBD is highly protein bound, and chronic use may produce accumulation of CBD in adipose tissues.[24]

Drug interactions

Several potential pharmacokinetic drug-drug interactions can occur with CBD with the probable implication in clinical management. CBD is metabolized in the liver by cytochrome P450 enzymes, and CBD bioavailability can be increased or decreased by exposure to strong enzyme inhibitor or inducer, respectively. CBD is a potent inhibitor of CYP2C19, CYP2D6, and CYP2C9, and serum levels of several antiepileptics such as clobazam, N-desmethylclobazam, topiramate, eslicarbazepine, zonisamide, and rufinamide increase with exposure to CBD. Elevated liver function result can occur with concomitant use of valproate and CBD without significant changes in the valproate levels. Drug interactions are summarized in Table 2.[25]

Clinical data

CBD oil has become the standard preparation because of the absence of smell and stigma associated with smoking of cannabis, the availability of a concentrated product for large-dose consumption, and the possibility of effective dosing by counting the number of drops. Several clinical studies of varying quality had been conducted over the years to understand the efficacy and safety of cannabinoid in the treatment of epilepsy. CBD-rich cannabis extracts were mostly used in earlier web-based surveys of patient or parents perspectives, but pharmaceutical-grade pure CBD oil was used in a recent physician-conducted exploratory study and the three published multinational blinded, randomized controlled trials.

In the 1930s and the 1940s, THC was first isolated from cannabis, and a study reported seizure freedom in one child of five from exposure to “THC isomers.” The first studies of pure CBD in the

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Table 2
Potential Drug Interactions

Enzyme and Substrates	Drug-Drug Interaction
Moderate or strong inhibitor of CYP3A4 or CYP2C19 (amiodarone, erythromycin, fluconazole, verapamil, etc.)	These can increase CBD plasma concentration
Strong CYP3A4 or CYP2C19 inducer (rifampicin)	These can decrease CBD plasma concentration
Substrates of UGT1A9 (e.g., diflunisal, propofol, fenofibrate)	CBD may inhibit the enzyme activity and increase the concentration of dosage of substrates
Substrates of UGT2B7 (e.g., gemfibrozil, lamotrigine, morphine, lorazepam)	CBD may inhibit the enzyme activity and increase the concentration of dosage of substrates
Clobazam	Level of the active metabolite of clobazam (N-desmethylclobazam) may increase by 5 fold, a potential for added benefit with an increased risk of side effects
Substrates of CYP2C8 (e.g., montelukast)	CBD may inhibit the enzyme activity and increase the concentration of the substrates
Substrates of CYP2C9 (e.g., phenytoin)	CBD may inhibit the enzyme activity and increase the concentration of the substrates
Substrates of CYP1A2 (e.g., theophylline, caffeine)	CBD may induce or inhibit the enzyme activity, and increase or decrease of the dosage may be necessary
Substrates of CYP2B6 (e.g., bupropion, efavirenz)	CBD may induce or inhibit the enzyme activity, and increase or decrease of the dosage may be necessary.

Abbreviation:
CBD = Cannabidiol

treatment of drug-resistant epilepsy date to the late 1970s and the 1980s.[26,27] In one study, four adults with epilepsy were exposed to 200 mg/day of oral CBD and compared with five adults who received placebo only.[28] In the CBD group, one individual became seizure free and another had partial improvement. None of the individuals who received the placebo experienced significant improvement. A six-month double-blind crossover study of 12 adults with refractory epilepsy failed to demonstrate a difference in the seizure frequency between 300 mg/day of CBD and placebo.[29] A Cochrane review in 2012 assessed the safety and efficacy of cannabinoid use in patients with epilepsy.[30] A total of four studies (blinded and unblinded randomized clinical trials) were included in the review; however, all of these trials lacked a large sample size. Moreover, there was no consistency in the products, dosages, dose frequency, or duration of treatment. It was determined that the efficacy of CBD in the treatment of epilepsy could not be confirmed, but a dose of 200 to 300 mg daily can be administered safely over a short period. Two of these studies were subsequently included in a systematic review by the American Academy of Neurology in 2014 to assess the role of medical marijuana in various neurological diseases such as multiple sclerosis, epilepsy, and movement disorders.[31] It was concluded that the data were inadequate to support or discredit the efficacy of cannabinoids for reducing seizure frequency.

The use of cannabinoids and specifically CBD has increased in response to several anecdotal reports of remarkable response in individuals with epilepsy and the perception that a substance or medicine derived from a natural source would be safer than other agents. A CNN special documentary “Weed” introduced a girl named Charlotte Figi with Dravet syndrome, who had medically intractable seizures and intellectual impairment. She had not responded to several earlier antiepileptic medications. At age five years, her mother started giving her a high-CBD cannabis extract (later called *Charlotte's Web*) made by the Stanley brothers in Colorado. In response to treatment with CBD oil, she had a remarkable improvement in seizure control and cognition.[32] This and other similar reports prompted many individuals to desperately seek CBD for the treatment of epilepsy.

Several articles derived from online surveys about the parental perception of the effectiveness of CBD have since been published, as well as a few retrospective chart reviews. A study by Porter et al. surveyed parents belonging to a Facebook group who were using CBD extracts to treat their child's seizures.[33] Of the 19 respondents (13 had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome [LGS] and idiopathic epilepsy), 16 (84%) reported a reduction of seizure frequency including two (11%) who achieved complete seizure freedom. A brief online survey by Hussain et al. included responses from 117 parents of children with epilepsy (including 53 with infantile spasms or LGS) to determine the perceived efficacy of CBD.[34] Eighty-five percent of all parents reported a reduction in seizure frequency, and 14% reported complete seizure freedom. Both of these online surveys noted other beneficial effects such as increased alertness and improved sleep and mood. However, as with any web survey, these studies may have significant selection bias, leading to inaccurate estimates. Press et al. retrospectively reviewed the medical records of 75 children and adolescents with epilepsy who were given oral cannabis extracts.[35] Their parents reported improvement of seizure frequency in 57% with greater than 50% reduction of seizures in 33% of the children. As with the previous two studies, improvement in behavior, alertness, speech, and motor skills were also reported in a subset of patients. A higher response rate was noted in patients with LGS and Dravet syndrome, but no patient with Doose syndrome responded favorably. However, background electroencephalographic abnormalities did not improve in patients who had better seizure control. Interestingly, 47% families who moved to Colorado for the treatment reported a favorable response compared with a 22% response rate reported by the families originally from Colorado, raising concern about potential reporting bias from heightened expectation and a stronger placebo effect.

Devinsky et al. reported the largest exploratory study of the efficacy and safety of CBD from an open-label, multicenter expanded access program in 214 patients aged one and 30 years with severe childhood-onset, drug-resistant epilepsy (33 patients with Dravet syndrome and 31 patients with LGS).[36] The median reduction in monthly motor seizures in 137 patients was 36.5% in this open-label trial.

With increasing interest in CBD's potential therapeutic use in epilepsy, three randomized controlled trials (RCT) were completed using a purified oral formulation of CBD. Devinsky et al. reported the findings of a double-blind, placebo-controlled trial that studied the effectiveness of CBD oil as an add-on agent compared with placebo in 120 children and young adults with treatment-resistant seizures and Dravet syndrome.[37] This study showed a statistically significant reduction in the frequency of convulsive seizures in the CBD group, in contrast to the placebo. The result of the research is summarized in Table 3. A significant weakness of the trial was the failure to report changes in the plasma concentration of clobazam and its active metabolite N-desmethylclobazam, the level of which can increase by fivefold with the concurrent use of CBD.[38] It is notable that 66% of patients in the CBD group were taking clobazam, and it is uncertain if the improvement in seizure frequency was due to a direct effect of CBD or an increased plasma level of N-desmethylclobazam.

The second published RCT was also a multicenter trial that investigated the efficacy of CBD (20 mg/kg/day) as an add-on therapy for drop seizures in 171 patients (aged two to 55 years) with treatment-resistant LGS.[39] This study monstrated a

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Table 3
Results of the Dravet Syndrome RCT[37]

Primary and Secondary End Points	CBD Oil	Placebo	*P* value
The decrease of median frequency of convulsive seizure per month	12.4-5.9	14.9-14.1	0.01
Percentage of patients with a >50% reduction in convulsive seizure frequency	43%	27%	0.08
Percentage of patients seizure free	5%	0%	0.08
The decrease in overall seizures per month	24-13.7	41.5-31.1	0.03
Improvement of the overall condition in at least one category Global Impression of Change	62%	34%	0.02

Abbreviations:
CBD = Cannabidiol
RCT = Randomized controlled trial

statistically significant reduction in the monthly number of drop seizures in the CBD group compared with the placebo group. Another RCT evaluated adjunctive CBD in 225 patients with LGS, comparing two doses (20 mg/kg/day and 10 mg/kg/day) of the purified CBD; this study demonstrated a significant reduction in drop seizures versus placebo with both doses.[40] The important findings of these RCTs are summarized in Table 4.

Smaller uncontrolled studies and case reports have suggested that CBD may be useful in the treatment of other forms of drug-resistant epilepsy and seizures. Hess et al. noted that about half of 18 patients with drug-resistant epilepsy secondary to tuberous sclerosis achieved greater than 50% reduction in seizure frequency, with a greater tendency for a positive response in those taking clobazam concurrently.[41] Gofshteyn et al. reported that six of seven children with febrile infection-related epilepsy syndrome experienced a decreased seizure frequency and duration after starting CBD.[42] Kaplan et al. reported that three of five patients with Sturge-Weber syndrome achieved greater than 50% seizure reduction in response to CBD.[43] Long-term efficacy and safety of CBD in an open-label expanded access program was reported in association with treatment-resistant seizures in four particularly severe childhood-onset epilepsies: CDKL5 deficiency disorder, Aicardi, Dup15q, and Doose syndromes.[44]

Data regarding long-term use is slowing accumulating. Szaflarski et al. reported significant improvements in adverse event profile, seizure severity, and seizure frequency after 12 weeks of treatment with CBD in an open-label add-on prospective study that were sustained over the 48-week duration of therapy.[45]

A recent meta-analysis of 11 previous studies comprising a population of 670 patients showed that 40% of the patients had more than a 50% reduction in seizure frequency after exposure to either CBD-rich cannabis extracts or pure CBD.[46] Interestingly, the average dose of pure CBD was over four times higher than that of CBD-rich cannabis extracts, and it was postulated that other phytocannabinoids present in the extract might contribute to its higher potency. Moreover, patients treated with CBD-rich extracts had less adverse events. However, as detailed above, studies involving cannabis extracts were done retrospectively and controlled studies with standardized cannabis extracts are necessary to confirm its superiority. McCoy et al. conducted a non-blinded trial of a cannabis plant extract in 20 children with Dravet syndrome and reported improved seizure control, decreased epileptiform activity on electroencephalography, and improved quality of life.[47]

Adverse drug reactions

In the Dravet syndrome trial, adverse events were reported in 93% patients in the CBD group and most commonly occurred during the first two weeks of the treatment. Common adverse events were fatigue, decreased appetite, somnolence, vomiting, and diarrhea. Serious adverse events (status epilepticus, elevated liver enzymes) were noted in 10 patients, and eight patients withdrew from the study. In the first LGS trial, common adverse events were similar to those in the Dravet study and occurred in 86% (74 of 86) patients, and 14% of the patients withdrew from the study due to liver enzyme elevation. Somnolence was more commonly reported when used in association with clobazam. In the above-mentioned controlled studies for LGS and Dravet syndrome, a much higher incidence of liver enzyme elevation was seen in the CBD group compared with the placebo group (13% versus 1%). This laboratory abnormality was typically detected during the first two months after treatment initiation and was primarily dose related; however, delayed transaminase elevations have also been noted, particularly with concomitant valproate use. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate. In these studies, transaminase elevation was reversible with discontinuation or reduction of CBD oil

Table 4
Results of the LGS RCTs[39,40]

Outcomes	CBD -20 mg/kg	Placebo	*P* value	20 mg/kg CBD Dose	10 mg/kg CBD Dose	Placebo	*P* value*
Median percentage reduction in monthly drop seizure frequency	43.9%	21.8%	0.0135	41.9%	37.2%	17.2%	0.005 & 0.002
Patients with at least a 50% reduction in drop seizures	44%	24%	0.0043	39%	36%	14%	<0.001 & 0.003
Number of patients seizure free from day 15 onward	3	0		5	3	1	N.A
Decrease in monthly frequency of total seizures	41.2%	13.7%	0.005	38.4%	36.4%	18.5%	0.009 & 0.002
The decrease in monthly frequency of non–drop seizures	49.4%	22.9%	0.0044	56.3%	66.7%	32.4%	NA
Improvement of overall condition	58%	34%	0.0012	57%	66%	44%	0.04 & 0.002

Abbreviations:
CBD = Cannabidiol
LGS = Lennox-Gastaut syndrome
NA = Not applicable
RCT = Randomized controlled trial
* *P* value: Between the 20 mg/kg CBD dose and placebo group & 10 mg/kg CBD group and the placebo group, respectively.

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and/or concomitant valproate. Higher baseline transaminase levels can promote further elevation of enzymes. Prescribing information for the newly FDA-approved pharmaceutical-grade CBD oil recommends obtaining hepatic enzymes and total bilirubin levels before starting treatment and then at frequent intervals up to six months. Further long-term studies are necessary to understand the potential for CBD to cause chronic liver and kidney injury. Moreover, animal studies are needed to determine CBD's effect on the embryo and on fetal development, pre- and postnatal development, and its potential toxicity on the juveniles. Recently, Russo et al. reported DNA damage in human liver cell line and buccal-derived cells from a low dose of CBD, which raised concern about potential carcinogenicity.[48] Further research related to carcinogenesis, pharmacokinetic properties, and pregnancy outcomes will also be necessary.

Indication

The US Food and Drug administration (FDA)-approved pharmaceutical-grade CBD is available as an oral solution (100 mg CBD/mL) to be used for the treatment of seizures in patients older than two years with Dravet syndrome or LGS.

Warnings and precautions

After the FDA approval of pharmaceutical-grade CBD oil in patients with LGS and DS, the Drug Enforcement Agency reclassified pharmaceutical-grade CBD (no more than 0.1% THC) as a schedule V agent. However, other CBD products remain as a Schedule I substance under the Controlled Substances Act. FDA-approved pharmaceutical-grade CBD oil is expensive, and insurance companies may approve it only for the designated indications. In despair, many families may resort to unregulated medical cannabis products in an attempt to control the seizures of their children.

Unfortunately, many of these products are developed with no regulation, quality assurance, or accurate content labeling. Buyers may not be particularly attentive to the actual CBD concentration of the purchased product and consume a very dilute solution, which is unlikely to provide a therapeutic effect. Unregulated CBD extracts may also have high THC concentrations. For example, Crippa et al. reported two children with treatment-resistant epilepsy who had improvement after the introduction of CBD extracts followed by seizure worsening after a short time with associated signs of toxicity from THC.[49] In both children, the toxicity resolved and seizure remission rapidly occurred when purified CBD replaced the extract with no THC.

The pharmacological potency of THC is much higher than that of CBD, and it can produce toxicity in a much smaller dose. This highlights the need for well-standardized formulations with fixed high CBD and low THC concentrations for the treatment of epilepsy. In some countries, well-standardized products are available. For example, available medical cannabis products approved for epilepsy in Israel have standardized CBD/THC ratios with the higher CBD ratio preparation being favored for the treatment of epilepsy.[50] It is essential that formulations have a very low THC content, as the antiseizure activity of THC is equivocal and can potentially aggravate seizures; moreover, it can be associated with short-term impairment in memory, motor coordination, and judgment. In addition, deleterious long-term effects including addiction, altered structural and functional connectivity in the brain, poor educational attainment, cognitive impairment, and diminished life satisfaction had been reported.[51] Neurologists must be aware of the intoxication effects of THC including mild euphoria, ataxia, decreased attention, red eyes, and possible seizure worsening in patients exposed to crude CBD extracts.

The evolving legislation and the increased use of cannabinoid products with little or no regulation or medical oversight may increase the risk of accidental ingestion, increased emergency room visits, and increased call volumes at poison control centers. Strict regulation in manufacturing, packaging, and labeling is warranted to ensure safe administration, but in many cases, unregulated products may be marketed and sold via the internet.

Despite significant advancements in clinical research on CBD, practitioners' attitudes regarding its use is divided. Klotz et al. published a cross-sectional survey to understand the current use of CBD among European practitioners treating children and adolescents for epilepsy.[52] They noted that most physicians received enquiries about CBD treatment regularly, but only 45% of them reported previous or current use of CBD and only 48% of the prescribers had used purified CBD rather than preparations containing THC. Limited individual experience was noted, with a single provider writing an average of only three prescriptions of CBD. In another survey, physicians were observed to be more suspicious of the safety of cannabis product compared with the general public.[53] In an Australian study, initiation of medical cannabis and weaning of other seizure medicines were often done without adequate medical consultation.[54] In general, there is a significant lack of consolidated perspectives among physicians including neurologists about the medicinal use of cannabis in general.

Conclusion

In summary, good-quality RCTs have shown a positive effect of CBD in Dravet syndrome and LGS. However, clarification of the independent effects of CBD therapy and a clobazam comedication effect needs to be addressed. Controlled studies are required to determine the effectiveness of CBD in new-onset seizures, other epilepsy syndromes, and refractory focal seizures. Controlled, randomized trials have revealed that the actual reduction in seizure frequency in response to CBD is comparable to that achieved in response to other antiepileptic drugs and have failed to meet the 80% to 85% responder rates in unblended web-based surveys based on parental reports.

Moreover, a high rate of adverse effect was noted in the controlled studies. CBD is far from a miracle cure, and it is of paramount importance to have a reasonable expectation of its usefulness as an antiepileptic medication. The misconception that CBD is free of adverse effects may be attributed to its derivation from a natural source. Adequate medical oversight is needed to monitor and manage the proper dose, side effects, the validity of the product, and potential drug-drug interactions. Neurologists should be attentive to the legislative changes at the state and federal levels and educate people about the differences between prescription CBD oil and medical marijuana.

References

1. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–286.
2. Chen SY, Wu N, Boulanger L, Sacco P. Antiepileptic drug treatment patterns and economic burden of commercially-insured patients with refractory epilepsy with partial onset seizures in the United States. J Med Econ. 2013;16:240–248.
3. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. Epilepsy Behav. 2017;70:298–301.
4. Consroe P, Benedito MA, Leite JR, Carlini EA, Mechoulam R. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. Eur J Pharmacol. 1982;83:293–298.
5. Klein BD, Jacobson CA, Metcalf CS, et al. Evaluation of cannabidiol in animal seizure models by the Epilepsy Therapy Screening Program (ETSP). Neurochem Res. 2017;42:1939–1948.

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6. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther. 2010;332:569–577.
7. Consroe P, Wolkin A. Cannabidiol–antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. J Pharmacol Exp Ther. 1977;201:26–32.
8. Gobira PH, Vilela LR, Goncalves BD, et al. Cannabidiol, a Cannabis sativa constituent, inhibits cocaine-induced seizures in mice: possible role of the mTOR pathway and reduction in glutamate release. Neurotoxicology. 2015;50:116–121.
9. Jones NA, Glyn SE, Akiyama S, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. Seizure. 2012;21:344–352.
10. Chiu P, Olsen DM, Borys HK, Karler R, Turkanis SA. The influence of cannabidiol and Δ9-tetrahydrocannabinol on cobalt epilepsy in rats. Epilepsia. 1979;20:365–375.
11. Val-da Silva D, Raquel A, Peixoto-Santos JE, et al. Protective effects of cannabidiol against seizures and neuronal death in a rat model of mesial temporal lobe epilepsy. Front Pharmacol. 2017;8:131.
12. Campbell CT, Phillips MS, Manasco K. Cannabinoids in Pediatrics. J Pediatr Pharmacol Ther. 2017;22:176–185.
13. Taylor AL. Addressing the global tragedy of needless pain: rethinking the United Nations single convention on narcotic drugs. J Law Med Ethics. 2007;35:556–570.
14. Cerdá M, Wall M, Keyes KM, Galea S, Hasin D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. Drug Alcohol Depend. 2012;120:22–27.
15. Svrakic DM, Lustman PJ, Mallya A, Lynn TA, Finney R, Svrakic NM. Legalization, decriminalization & medicinal use of cannabis: a scientific and public health perspective. Mo Med. 2012;109:90.
16. Abraham B. Uttarakhand To Become First Indian State To Legalise Cannabis Cultivation. Indiatimes. Available at: https://www.indiatimes.com/news/india/uttarakhand-to-become-first-indian-state-to-legalise-cannabis-cultivation-247769.html. Accessed October 31, 2018
17. Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annu Rev Psychol. 2013;64:21–47.
18. Todd SM, Arnold JC. Neural correlates of interactions between cannabidiol and Δ9-tetrahydrocannabinol in mice: implications for medical cannabis. Br J Pharmacol. 2016;173:53–65.
19. Bih CI, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ. Molecular targets of cannabidiol in neurological disorders. Neurotherapeutics. 2015;12:699–730.
20. Jiang R, Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. Drug Metab Pharmacokinet. 2013;28:332–338.
21. Zendulka O, Dovrtelová G, Nosková K, et al. Cannabinoids and cytochrome P450 interactions. Curr Drug Metab. 2016 Mar 1;17:206–226.
22. Sativex. Summary of Product Characteristics (March 2015 revision) [Internet]. Newbury: GW Pharma Ltd, [cited 2017 Jul 6]. Available at: https://www.medicines.org.uk/emc/medicine/23262. Accessed October 31, 2018.
23. Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav. 1991;40:701–708.
24. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII). Epilepsia. 2017;58:181–221.
25. Epidiolex prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf. Accessed October 28, 2018.
26. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980;21:175–185.
27. Ames FR. Anticonvulsant effect of cannabidiol. S Afr Med J. 1986;69:14.
28. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften. 1978;65:174–179.
29. Trembly B., and Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. In: Marijuana '90 International Conference on Cannabis and Cannabinoids, Kolympari, Crete, July 8–11, 1990.
30. Gloss D, Vickrey B. Cannabinoids for epilepsy. The Cochrane Library; 2014.
31. Koppel BS, Brust JC, Fife T, et al. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82:1556–1563.
32. Gupta S. Why I changed my mind on weed. CNN Com. 2013:9.
33. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 2013;29:574–577.
34. Hussain SA, Zhou R, Jacobson C, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox–Gastaut syndrome. Epilepsy Behav. 2015;47:138–141.
35. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav. 2015;45:49–52.
36. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016;15:270–278.
37. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. New Engl J Med. 2017;376:2011–2020.
38. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015;56:1246–1251.
39. Thiele EA, Marsh ED, French JA, et al, GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018:1085–1096.
40. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. New Engl J Med. 2018;378:1888–1897.
41. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016;57:1617–1624.
42. Gofshteyn JS, Wilfong A, Devinsky O, et al. Cannabidiol as a potential treatment for febrile infection-related epilepsy syndrome (FIRES) in the acute and chronic phases. J child Neurol. 2017;32:35–40.
43. Kaplan EH, Offermann EA, Sievers JW, Comi AM. Cannabidiol treatment for refractory seizures in Sturge-Weber syndrome. Pediatr Neurol. 2017;71:18–23.
44. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav. 2018;86:131–137.
45. Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. Epilepsy Behav. 2018.
46. Pamplona FA, da Silva LR, Coan AC. Potential clinical benefits of CBD-rich Cannabis extracts over purified CBD in treatment-resistant epilepsy: observational data meta-analysis. Front Neurol. 2018;9.
47. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. Ann Clin translational Neurol. 2018.
48. Russo C, Ferk F, Mišík M, et al. Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells. Arch Toxicol. 2019;93:179–188, 1-0.
49. Crippa JA, Crippa A, Hallak JE, Martín-Santos R, Zuardi AW. Δ9-THC intoxication by cannabidiol-enriched cannabis extract in two children with refractory epilepsy: full remission after switching to purified cannabidiol. Front Pharmacol. 2016;7:359.
50. Hausman-Kedem M, Kramer U. Efficacy of medical cannabis for treating refractory epilepsy in children and adolescents, with emphasis on the Israel experience. Isr Med Assoc J. 2017;19:76–78.
51. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. New Engl J Med. 2014;370:2219–2227.
52. Klotz KA, Schulze-Bonhage A, San Antonio-Arce V, Jacobs J. Cannabidiol for Treatment of Childhood Epilepsy—a cross-sectional Survey. Front Neurol. 2018.
53. Mathern GW, Beninsig L, Nehlig A. Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: result of Epilepsia's survey. Epilepsia. 2015;56:1–6.
54. Suraev AS, Todd L, Bowen MT, et al. An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use. Epilepsy Behav. 2017;70:334–340.

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