Cannabis, Cannabidiol, and Epilepsy

Clinical Considerations and Practical Applications

A new frontier brings new questions and old dilemmas.

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Background

As early as 12,000 BCE, texts from central Asia reported human use of cannabis for non-medical indications including ropes, fibers, and cloth. Ancient Chinese manuscripts from approximately 10,000 years later give the first documented use of cannabis for medical purposes.[1] Other early reports from ancient Mesopotamia, Persia, and India describe cannabis use for indications such as spasticity, depression, anxiety, and epilepsy.[1,2]

Cannabis for medicinal purposes was not scientifically studied until the 19th century. In 1840, William O'Shaughnessy documented efficacy of cannabis for treating babies with infantile convulsions and studied cannabis's effect in patients with epilepsy, spasticity, and arthritis. Cannabis and its various components, namely δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have continued to be researched.[3] In recent years, use of CBD for treating patients with refractory epilepsies has come to the forefront, increasing research and resulting in the first Food and Drug Administration (FDA)-approved CBD-based medication for patients with epilepsy.

With this new frontier in modern medicine, practitioners are faced with new questions and old dilemmas. Use of medical marijuana and CBD are becoming increasingly common, but there is still much to be discerned in the realm of evidence-based medicine. Several recent randomized controlled trials of CBD have shown efficacy in a standardized, controlled manner allowing the data to be adjudicated scientifically and applied practically. With solid data for physicians to justify therapeutic plans that include CBD, the horizons for our patients with epilepsy have expanded. Practitioners, then, must also look to the horizon and expect unforeseen hurdles before the place for CBD is ultimately found. Furthermore, CBD is one cannabinoid amongst more than 100 within the cannabis plant. We can expect subsequent research to broaden the indications and availability of other cannabis-based compounds in the future.

Mechanism of Action

The endocannabinoid system, which may play a role in epileptogenesis, includes 2 G-protein coupled receptors (cannabinoid type 1 [CB1] and cannabinoid type 2 [CB2]) and 2 endogenously synthesized, lipid-signaling endocannabinoids (anandamide [*N*-arachidonyl ethanolamide] and 2-arachidonoyl glycerol [2-AG]) that bind to CB1 and CB2. A presynaptic receptor, CB1 is highly expressed in the hippocampus, amygdala, cingulate, cerebral cortex, basal ganglia, midbrain, and medulla. Therapeutic effects of CB1 binding are via modulation of neurotransmitter release, including dopamine, GABA, glutamine, serotonin, norepinephrine, and acetylcholine. Concentrated in peripheral immune tissues (i.e. spleen, bone marrow, B-cells, macrophages), CB2 receptors have limited expression in the brainstem and hippocampus. In the context of seizures and epilepsy, although it seems CB1 would be a likely target, that does not appear to be the case.

Cannabis contains more than 100 unique compounds called phytocannabinoids, which are quite similar to lipophilic endocannabinoids—differentiated only by the origin of synthesis (ie, plants). The 2 primary phytocannabinoids are THC and CBD.[3,5] A direct agonist of the CB1 and CB2 receptors, the psychoactive effect of THC is secondary CB1 activation. There are mixed reports of seizure treatment success and seizure exacerbation.[3,5] Unlike THC, CBD does not directly agonize CB1 receptors and subsequently is not psychoactive. Some believe this is a benefit as it may have less potential for abuse. CBD's mechanism of action is not fully elucidated yet and appears to be related to its effects on serotonergic and GABAergic activity, intracellular calcium modulation, and potential anti-inflammatory effects. CBD is highly lipophilic and becomes distributed in the brain rapidly.[3-6]

Much remains to be ascertained regarding cannabis and its precise mechanism(s) of action in epilepsy. Evidence suggests that in addition to THC and CBD other components of cannabis may have anticonvulsant properties (eg, δ-9-tetrahydrocannabivarin [THCV], cannabidivarin [CBDV], δ-8-tetrahydrocannabinol [δ-8-THC], and cannabinol [CBN].[4] Only time and additional scientific effort will help discern their potential as medications.

Reports of Therapeutic Efficacy

There are a handful of notoriously refractory epilepsy syndromes for which CBD has reported efficacy; most frequently cited are Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS), with the most scientifically rigorous data coming from studies of pharmaceutical-grade CBD (Epidiolex, Greenwich Biosciences, Carlsbad, CA) (Table 1).

In clinical trials, pharmaceutical-grade CBD treatment (20 mg/kg/day) of pediatric patients with DS had a statistically significant reduction in the number of convulsive seizures per month (-38.9%, 12.4 seizures/month to 5.9 seizures/month) compared to those treated with placebo (-13.3%-14.9 seizures/month to 14.1 seizures/month, $P = .01$).[7] Notably, 8 patients dropped out of the treatment arm due to side effects compared to only 1 patient in the placebo group. Overall, most side effects were well tolerated. The majority of caregivers (62%) reported an overall improvement for children receiving pharmaceutical-grade CBD compared to that seen by parents of children given placebo (34%) ($P = .02$). This is significant both clinically and statistically as positive perception may positively affect patient outcomes[7]

In a similar study of children and adults with LGS, patients were treated with pharmaceutical-grade cannabidiol at doses of 10 mg/kg/day or 20 mg/kg/day. Both groups of patients treated had larger reductions in drop seizures (37.2% fewer [$P = .002$] and 41.9% fewer [$P = .05$], respectively) compared to patients given placebo (17.2% fewer).[8] These studies served as the basis for submission and ultimate approval by the FDA of pharmaceutical-grade CBD.

TABLE 1. STUDIES CITING EFFICACY OF CANNABIDIOL BY EPILEPSY SYNDROME.

Epilepsy Syndrome	Patient Ages	CBD Products and Dose	Range of Reported Efficacy	Study Type
Dravet syndrome	6 mos-18.25 y	Pharmaceutical grade[a] 5-20 mg/kg/day[7]	Median reduction of -38.9% in convulsive seizures per month	DB, PC, RCT
		Artisanal; 1-14 mg/kg/day[12]	0 to > 80% reduction in seizure frequency (majority of reports show at least 80% improvement)	Obs, Survey
		Artisanal; n/a[14]	Seizure reduction of >50% in 23% of patients	Ret, CR
Doose syndrome	6 mos-11 y	Artisanal <0.5-13 mg/kg/day[12]	0 to > 80% reduction in seizure frequency	Obs, Survey
		Artisanal; n/a[14]	Seizure reduction of >50% in 0% of patients	Ret, CR
		Pharmaceutical grade 8.8-27.5 mg/kg/day[9]	Median convulsive seizure decrease from baseline of 58.6%	OL, RCT
Lennox-Gastaut syndrome	6 mos-55 y	Pharmaceutical grade 10-20 mg/kg/day[8]	~36-38% median reduction in total seizures; ~37-42% median reduction in drop seizures; 54-61% median reduction in non-drop seizures	DB, PC, RCT
		Artisanal; n/a[12]	> 80% reduction in seizure frequency	Obs, Survey
		Artisanal 2.9-7.5 mg/kg/day[13]	Seizure reduction in 85% of the study population (14% with seizure freedom)	Obs, Ret, Survey
		Artisanal; n/a[14]	Seizure reduction of >50% in 58-89% of patients	Ret, CR
		Artisanal; n/a[24]	Seizure reduction of >50% in 58% to 89% of patients	Ret, CR
Tuberous sclerosis complex [10]	2-31 y	Pharmaceutical grade 5-50 mg/kg/day	~88% of patients had a reduction (-5.9 % to -100%) in weekly seizures at 3 months; median reduction of -48.8% at 3 months	EA, Obs, OL

Notes: a, Pharmaceutical grade refers to manufactured FDA-approved cannibinoid (Epidiolex; Greenwich Pharmaceuticals, Carlsbad, CA). Abbreviations: CR, chart review; DB, double-blinded; EA, expanded access; Obs, observational; OL, open-label; PC, placebo-controlled; RCT, randomized controlled trial; Ret, retrospective; y, years

A multicenter, open-label, prospective study examined the use of pharmaceutical-grade CBD as an adjunctive treatment for 55 patients with other treatment-resistant epilepsy syndromes (eg, Aicardi's, Dup15q, and Doose' syndromes).[9] Pharmaceutical-grade CBD appeared not only to be well tolerated (27% withdrawal rate), but also efficacious. Patients experienced statistically significant decreases in convulsive seizures per month after 12 weeks; this was sustained through week 48 of the study.[9]

In an open-label trial without a placebo arm for treatment of patients with refractory seizures in tuberous sclerosis complex (TSC), patients treated with pharmaceutical-grade CBD had a 50% response at the 3-month interval and largely maintained this through month 12. The largest effects were seen for tonic-clonic seizures (-91.4%), spasms (-87.5%), and atonic seizures (-86.5%); complex partial seizures with secondary generalization showed less response (-38.6%). Side effects were similar to previous reports (ie, drowsiness, ataxia, diarrhea).[10] An ongoing double-blind, placebo-controlled trial of pharmaceutical-grade CBD for patients with refractory seizures in TSC has completed enrollment and is in the data collection stage.

A large analysis of expanded access to pharmaceutical-grade CBD included 607 patients and 25 institutions.[11] Of these patients, 76% continued treatment at a mean of 48 weeks. Of those who discontinued therapy, 15% withdrew because of lack of efficacy and 5% withdrew due to adverse effects. With adjunctive CBD therapy, the number of median monthly convulsive seizures was reduced by 51% at 12 weeks and this was largely sustained through 96 weeks. Likewise, the total number of seizures per month was reduced by 48% at 12 weeks and similarly sustained through 96 weeks.[11]

Many other studies examining both artisanal and pharmaceutical-grade CBD show efficacy in patients with LGS, DS, and convulsive and atonic type seizures (Table 2).[12-14] Current data strongly support that pharmaceutical-grade CBD is efficacious for seizures classified as convulsive or drop type. Data are lacking for nonconvulsive seizures, which are more difficult to quantify; the studies discussed in this article were not designed to assess this endpoint.

Product Considerations

The majority of studies described in this article involve a single, standardized formulation of CBD created with cannabis grown and CBD extracted under extremely strict conditions, as would be required for any drug approved for human consumption. These processes create a reliable amount of highly concentrated CBD (~99.7%) from batch to batch to ensure purity, safety, and efficacy claims of the product.

There are a number of artisanal CBD products available from dispensaries and online retailers, many touting their efficacy for epilepsy and other conditions. Unlike the recently FDA-approved formulation, artisanal CBD products are considered supplements and do not have the same regulatory oversight. As a result, these products cannot be labeled to state claims of health benefit. The consumer must be aware these products may vary widely in contents and purity. A study examined the accuracy of CBD labeling on artisanal products and found that of 84 different CBD extracts reviewed.[26] (~31%) were accurate, 36 (~42%) were underlabeled (exceeded value by more than 10%) and 23 (~25%) were overlabeled (actual content at least 10% below reported value).[15]

This is not to say that artisanal cannabis products may not be efficacious for epilepsy. Practitioners simply need to be aware of the differences. Although there is good evidence for safety and efficacy of CBD, many artisanal products may contain high amounts of other cannabinoids for which research is lacking. Consequently, patient response and potential adverse effects are unknown and should be taken into consideration when discussing the risks and benefits of this type of therapy.

Dosing and Monitoring Considerations

The recommended starting dose of pharmaceutical-grade CBD is 2.5 mg per kg twice daily to be titrated up weekly intervals to a maintenance dose of 10 mg/kg/day and a maximum of 20 mg/kg/day.[16] Research supports this, and some even suggests doses of up to 50 mg/kg/day,[11,17] while acknowledging that with increased dosing there is an increased risk of side effects. In a study of patients with DS who were randomized to receive 5, 10, or 20 mg/kg/day of pharmaceutical-grade CBD, or placebo, 32 of 34 patients tolerated the drug and completed treatment, although higher doses were associated with a proportional increase in side effects.[17] Based on this report and other trials, doses of 5 to 20 mg/kg/day appear to balance efficacy with risks for potential side effects.

In the study that included 607 patients at 25 centers, 88% experienced some sort of side effect.[11] Severe side effects were reported in 33% of patients, the most common being convulsion (9%), status epilepticus (7%), pneumonia (5%), and vomiting (3%). Milder side effects included somnolence, fatigue, diarrhea, and reduced appetite.[11] Other reports validate these findings and report statistically significant instances of somnolence, decreased appetite, fatigue, and diarrhea in patients receiving pharmaceutical-grade CBD. More specifically, somnolence occurred in 22% to 36% of patients, diarrhea in 29% to 31%, decreased appetite in 20% to 28%, and fatigue in 20% to 22%.[7-9] Other notable side effects include convulsion, respiratory tract infections, weight loss, status epilepticus, irritability, and pyrexia, which appear to be dose-related and can be therapy-limiting.[7-9,11]

Hepatotoxicity has emerged as an adverse effect of CBD treatment of particular concern. Many antiepileptic drugs (AEDs) carry some risk of hepatotoxicity, but with a clear monitoring plan, this concern could be reduced. The manufacturer of pharmaceutical-grade CBD recommends discon-

TABLE 2. STUDIES CITING EFFICACY OF CANNABIDIOL BY SEIZURE TYPE.

Seizure Type	Patient Ages	CBD Products and Dose	Range of Reported Efficacy	Study Type
Absence[14]	6 mos- 18.25 y	Artisanal; n/a	Seizure reduction of >50% in 28% of patients	Ret, CR
Atonic	6 mos-31 y	Artisanal; n/a[14]	Seizure reduction of >50% in 44% of patients	Ret, CR
		Pharmaceutical grade[a] 5-50 mg/kg/day[10]	Seizure reduction of -86.5% at 3 months	EA, Obs, OL
Epileptic Spasms	6 mos-31 y	Artisanal; n/a[14]	Seizure reduction of >50% in 36% of patients	Ret, CR
		Pharmaceutical grade 5-50 mg/kg/day[10]	Seizure reduction of -87.5% at 3 months	EA, Obs, OL
Focal	6 mos-18.25 y	Artisanal; n/a[14]	Seizure reduction of >50% in 38% of patients	Ret, CR
GTC	6 mos-31 y	Artisanal; n/a[14]	Seizure reduction of >50% in 30% of patients	Ret, CR
		Pharmaceutical grade 5-50 mg/kg/day[10]	Seizure reduction of -91.4% at 3 months	EA, Obs, OL
IS[13]	3-10 y	Artisanal; 2.9-7.5 mg/kg/day[13]	Seizure reduction in 85% of the study population (14% with seizure freedom)	Obs, Ret, Survey
Myoclonic14	6 mos-18.25 y	Artisanal; n/a	Seizure reduction of >50% in 20% of patients	Ret, CR
Tonic	6 mos-31 y	Artisanal; n/a[14]	Seizure reduction of >50% in 17% of patients	Ret, CR
		Pharmaceutical grade[a] 5-50 mg/kg/day[10]	Seizure reduction of -48.2% at 3 months	EA, Obs, OL

Notes: a, Pharmaceutical grade manufactured FDA-approved drug (Epidiolex; Greenwich Pharmaceuticals, Carlsbad, CA).
Abbreviations: IS, Infantile Spasms; GTC, generalized tonic clonic; CR, chart review; DB, double-blinded; EA, expanded access; Obs, observational; OL, open-label; PC, placebo-controlled; RCT, randomized controlled trial; Ret, retrospective; y, years.

tinuation if liver function test (LFT) levels rise to 3 times the upper limit of normal (ULN) and bilirubin levels are twice or more the ULN.[16] If patients experience sustained LFT elevation more than 5 times the ULN, CBD treatment should be discontinued. Elevation of LFTs appears to be most common in the first 2 months of treatment but has also been observed in later stages of treatment. Liver monitoring is recommended at months 1, 3, and 6 after initiating treatment with pharmaceutical-grade CBD or monthly after dose changes or addition of another AED that interacts with CBD.[16]

The hepatotoxicity risk of pharmaceutical-grade CBD appears to be more common if there is polypharmacy with valproic acid products or clobazam, although LFT elevation has also been shown to occur without these concomitant drugs.[17-19] Some have postulated that interaction with liver enzymes may contribute to the positive therapeutic effects seen in clinical trials of pharmaceutical-grade CBD.[13,20,21] There are several other pertinent interactions to consider when implementing CBD treatment for patients with epilepsy. Varying reports of alterations in serum concentration of rufinamide, topiramate, zonisamide, and eslicarbazepine have also been noted.[17,18] Topiramate and rufinamide both appear to have dose-related increases in serum concentrations in the presence of CBD whereas the serum increases of zonisamide and eslicarbazepine were present to a lesser extent.[17,18, 20]

It is likely many of the discussed interactions are related to the effect of CBD on CYP enzyme activity. Strong CYP3A4 or CYP2C19 inhibitors and inducers appear to increase and decrease CBD serum concentrations, respectively.[16] It is wise for practitioners to be especially careful when initiating CBD in patients with epilepsy on concomitant valproic acid or clobazam because these combinations could put patients at a higher risk for hepatotoxicity, drug interactions, and secondary side effects related to subsequent toxicity (eg, sedation, decreased efficacy, and breakthrough seizures). Close monitoring may be encouraged or even required.

Legal and Financial Considerations

In the context of CBD and its role in medicine in the US, approval of pharmaceutical-grade CBD represents a paradigm shift. Alone, CBD has no schedule designation, but as a component of marijuana, it has been listed as a schedule I drug—defined by the Drug Enforcement Administration (DEA) as a substance having high potential for abuse with no medical efficacy.[3] Now that the FDA has approved a CBD product for medicinal use, it is inherently assumed CBD does, indeed, have medical efficacy and requires rescheduling. This will occur imminently in the US prior to expected release of pharmaceutical-grade CBD in late 2018. How this will affect the legality of artisanal CBD products is less clear, as many may contain unac-

ceptable amounts of THC and other cannabinoids which are likely to remain schedule I until there is more evidence for safety and efficacy. Cannabis law varies widely across the US from state to state, further complicating procurement for patients choosing not to use the FDA-approved product.

CBD and marijuana laws vary internationally as well. Several countries allow utilization of cannabis for medical purposes, but the cultivation and possession of marijuana for recreational use remains largely illegal. In the United Kingdom, once pharmaceutical-grade CBD is approved, lawmakers plan to re-examine current laws to allow for legal utilization of this CBD product.[22] Similar to patients in the United States, those in the United Kingdom and Europe will likely gain increased access to CBD as a legitimate treatment option in the near future.

The cost of treatment is another factor that warrants discussion. Currently, CBD oils procured from dispensaries are not covered by health insurance as they lack accepted evidence of efficacy. These oils may place a burden of $100-$600 per month depending on the patient's dose which often is lower than that shown effective in the placebo-controlled trials.[23] If doses are titrated similarly to those trials, costs often approach $1,500-$3,000 per month for an average-sized adult. Pharmaceutical-grade CBD will likely be covered by insurance for indicated patients based on FDA approval with the average estimated cost of $32,000 per year without insurance.[24]

Conclusions

Cannabis and CBD have a long history of use for medical purposes throughout human history. Until recently, standardized studies with large datasets have been lacking. Now, with the change in social climate and attitude towards the potential of cannabis and CBD, data are amassing to provide much-needed insight into the practical application of CBD in patients with seizures and epilepsy.

In patients with refractory epilepsy syndromes—especially in those characterized by convulsive and "drop attack" seizures—CBD is a promising adjunctive alternative treatment. More studies are needed to determine the exact mechanism of therapeutic efficacy (ie direct antiepileptic target vs. optimization of concomitant medications), but in the meantime appears to be reasonably safe and efficacious.

Practitioners still must be cognizant of individual patient factors because CBD is not a benign entity. Vigilance for concomitant hepatotoxic antiepileptics, potential interactions, and side-effects must be maintained and cost and variability between different formulations considered. New options are on the horizon and expanding potential medical treatment with CBD. Governmental acceptance of a CBD-based product is helping to open doors for many families and patients with previously limited options. The CBD safety and efficacy profiles combined with the great need for better treatment options in refractory epilepsy make this a promising therapy for patients and practitioners alike. We are likely experiencing the first among many therapies to be derived from the cannabis plant in the coming years. ■

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Disclosures

MSP has received honorarium for consulting from Compassionate Cultivation and serves as the site PI for several phase III studies of cannibidiol sponsored by Greenwich Biosciences. The authors have no other financial or other relationships or conflicts to disclose.