The case for assessing cannabidiol in epilepsy

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Summary

Intractable epilepsies have an extraordinary impact on cognitive and behavioral function and quality of life, and the treatment of seizures represents a challenge and a unique opportunity. Over the past few years, considerable attention has focused on cannabidiol (CBD), the major nonpsychotropic compound of *Cannabis sativa*. Basic research studies have provided strong evidence for safety and anticonvulsant properties of CBD. However, the lack of pure, pharmacologically active compounds and legal restrictions have prevented clinical research and confined data on efficacy and safety to anecdotal reports. Pure CBD appears to be an ideal candidate among phytocannabinoids as a therapy for treatment-resistant epilepsy. A first step in this direction is to systematically investigate the safety, pharmacokinetics, and interactions of CBD with other antiepileptic drugs and obtain an initial signal regarding efficacy at different dosages. These data can then be used to plan double-blinded placebo-controlled efficacy trials.

KEY WORDS: **Epilepsy, Childhood, Cannabidiol.**

Epilepsy can harm the brain, especially during development, and is often associated with cognitive, behavioral, and psychiatric comorbidities that can combine to severely impair quality of life.[1,2] Epilepsy onset before age 3 years and pharmacoresistance with uncontrolled seizures are associated with lower IQ later in life.[3] In older children and adults, epilepsy is also a serious disorder with comorbidities including stigma, restrictive lifestyle, cognitive and psychiatric disorders, physical injuries, and mortality due to sudden unexpected death, drowning, accident, and suicide.

Recently, two compounds derived from the marijuana plants *Cannabis sativa* or *Cannabis indica*—Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)—have attracted significant research interest as potential therapies for epilepsy. THC is the major psychoactive component of marijuana due to its role as a partial agonist at cannabinoid 1 (CB_1) receptors, which are located primarily in the brain; it is also a partial agonist of CB_2 receptors, which are located primarily in immune and hematopoietic cells. CB_1 receptors are present in inhibitory γ-aminobutyric acid (GABA)ergic and excitatory glutamatergic neurons.[4] CBD is the major nonpsychoactive component of cannabis and can diminish the effects of CB_1 activation. The mechanism by which CBD exerts its antiepileptic effects is not well defined, and likely includes multiple mechanisms. These may include modulation of equilibrative nucleoside transporter, the orphan G-protein-coupled protein receptor, and the transient receptor potential of melastatin type 8 channel.[5] CBD is an agonist at the 5-HT_{1a} and the α3 and α1 glycine receptors and the transient receptor potential of ankyrin type 1.[6] At higher concentrations, CBD activates the nuclear peroxi-

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some proliferator-activated receptor-γ and the transient receptor potential of vanilloid type 1 (TRPV1) and TRPV2 channels, and inhibits the cellular uptake and degradation of the endocannabinoid anandamide.[7] CBD also modulates the intracellular Ca^{2+} concentration and inhibits T-type calcium channels.[8] In addition, CBD has antiapoptotic, neuroprotective, and antiinflammatory effects.[9]

In animal models of seizures and epilepsy, Δ^9-THC has primarily anticonvulsant properties, but is proconvulsant in some species;[10] CBD is more consistently anticonvulsant.[11] Many effects of CBD follow a bell-shaped dose–response curve,[12–14] suggesting that dose is a key factor in its pharmacology.

Recently, CBD has proven to have anxiolytic effects in a randomized controlled trial (RCT),[15] and it is has been proposed as a potential treatment for psychosis.[16]

Early clinical studies on the use of CBD and other cannabinoids for epilepsy had methodologic limitations. A recent Cochrane review identified four studies published between 1978 and 1990 that met the inclusion criteria of being RCTs that were blinded (single or double) or unblinded.[17] These studies were not adequately powered (they included between 9 and 15 patients), one of them being an unpublished abstract.[17] Therefore, they failed to provide evidence about cannabinoid efficacy in treating epilepsy. The main conclusion was that CBD in the 200–300 mg/day range in adults is usually well tolerated, although, given the short lengths of treatment reported, no information could be obtained regarding the safety of long-term CBD treatment.[17]

Clinical research on CBD in epilepsy has been limited by the legal restriction to use cannabis-derived medicine. Although CBD does not seem to have the psychoactive properties associated with THC,[18] U.S. federal law prohibits its use and it is classified as a Schedule I controlled substance. Paradoxically, marijuana with Δ^9-THC, is available in about one third of the states in the United States for medical use and there are many more states that are currently considering legislation to approve "medical" marijuana; it is also licensed in Canada and European countries such as the The Netherlands and Israel. Many physicians who treat epilepsy have encountered patients using cannabis preparations as an alternative therapy as patients and parents have sought CBD-enriched cannabis for treatment-resistant epilepsy.

A recent U.S. survey of 19 parents, 12 of whom had children with Dravet syndrome, explored the use of CBD-enriched cannabis in pediatric treatment-resistant epilepsy.[19]

Of parental respondents, 53% reported a >80% reduction in seizure frequency; 11% of children were seizure free during a 3-month trial. Among the 12 patients with Dravet syndrome, 42% reported a >80% reduction in seizures. The parents often reported improved alertness and none reported severe side effects, although a few of them reported drowsiness and fatigue. Neither the doses nor the exact composition of the different cannabis extracts could be determined. Therefore, a possible placebo effect as well as the impact of the percentages of THC on both effects and side effects in this very select population could not be assessed.

Prominent Internet and national media attention has fueled a rapidly growing interest among parents to use cannabis-derivatives to treat epilepsy. The data consist of anecdotal cases of children successfully treated with the medical marijuana, often CBD-enriched preparations. However, the lack of regulation and standardization in the medical cannabis industry raises concerns regarding the composition and consistency of the products that are dispensed. Most parents use cannabis extracts purchased from a dispensary or from a cannabis grower.[19] These artisanal preparations may contain different percentages of CBD and THC, as well as many other cannabinoids and other compounds. Their concentration can vary based on the plant clones, weather, soil, and other factors. Most importantly, there are no controlled data on the use of these preparations. We lack blinded data on efficacy as well as safety. To assess safety and efficacy of medical marijuana, the chemical mixture should be stable over time and by different growers. For example, a high CBD:THC clone by a grower in one area may have different ratios of these two cannabinoids as well as varying quantities of other cannabinoids when cultivated by another grower in another area. And there may be variability even for the same grower because soil nutrients, plant pathogens, and many other factors can vary even within the same greenhouse.

Randomized double-blind placebo-controlled trials are required to determine the efficacy of CBD, CBD-THC combinations, or other cannabis products as potential treatments for epilepsy. Anecdotal data of individual cases or case series can give a potential signal of efficacy and safety, but doctors, patients, and parents are all biased. A strong selection bias can lead patients and parents who have heard positive information about the efficacy of medical marijuana and who believe in the benefits of a "naturalistic therapy" to use marijuana as an epilepsy therapy. The risk of negative effects of cannabis in the developing brain must be considered. Recent studies suggest that cannabis has adverse effects in children younger than age 15 years, including a risk for psychosis,[20] and long-term impairment of executive function.[21] Although many marijuana strains used for epilepsy treatment are reported to have high CBD:THC ratios, THC is more potent than CBD, so low doses of THC can have adverse effects, especially in young children. In addition to THC and CBD, there are >80 other cannabinoids and 300 noncannabinoid chemicals present in cannabis. The safety of these chemicals should be studied. Moreover, the belief that treatments derived from natural products are safer or more effective is common and potentially dangerous. For example, tetrodotoxin is a "natural" sodium

channel blocker produced by fish, worms, octopi, crabs, and other animals. It is 100 times more lethal than potassium cyanide. Many natural products and synthetic medications vary in their therapeutic versus toxic effect based on dose as well as genetic and nongenetic (e.g., other medications) factors.

Autonomy is not a compelling argument in our view. "A naturally occurring and effective herbaceutical has power for a patient or parent to improve health through self-help and self-healing."[22] Many natural botanical compounds are toxic (e.g., THC in children) and many more have no therapeutic or only harmful effects. Autonomy is a step backward for medical care if it becomes dissociated from rigorous and unbiased study. What if the parents of a child with acute leukemia abandoned the "chemical cocktail" of oncologists with >90% cure rates for a herbaceutical for which a group of parents claimed equal efficacy but no side effects? Laetrile was a natural compound widely hailed as an effective cancer treatment; many patients took laetrile instead of proven chemotherapeutic agents. When the objective data came in, the only clear effect was cyanide toxicity due to metabolism of a compound often contained in the pits used to obtain laetrile.[23] The best track record in medicine is with pure compounds and rigorous data. Combination therapies such as CBD and THC are effective for disorders such as spasms in patients with multiple sclerosis, but there is little controlled data for efficacy in any disorder using whole plant extracts.

Pure CBD appears to be an excellent candidate among phytocannabinoids to evaluate in patients with treatment-resistant epilepsy.[9,24] Its lack of THC and therefore of the risks associated with the use of marijuana in the young age,[25,26] its excellent safety profile in humans, as well as its efficacy in preclinical studies suggest that it could be a safe and effective drug for epilepsy. The anecdotal human experiences reported in patients with Dravet syndrome and Lennox-Gastaut syndrome[19] are with products containing primarily CBD, often with CBD:THC ratios as high as >20:1. Nevertheless, the safety and efficacy of CBD in patients with epilepsy need to be determined.

Patients, families, and the medical community need objective and unbiased data on safety and efficacy to endorse a new drug to treat epilepsy. To assess safety and efficacy, we need to define the precise chemical profile of a drug or botanical product. The data currently available for medicinal marijuana do not meet these criteria.[27] In addition, adequate pharmacokinetic data are needed to inform dosing recommendations and identify interactions with antiepileptic drugs (AEDs) and other medications that can cause toxicity or impair efficacy.

A reasonable development program for CBD in the treatment of epilepsy will obtain initial observations from a dose-tolerability and pharmacokinetic study. This will provide data on safety, time to peak level, half-life, drug interactions, as well as obtain a signal on potential efficacy and dose-response. Subsequently, prospective RCTs should be carried out in select populations of patients with treatment-resistant epilepsies. Dravet syndrome and Lennox-Gastaut syndrome are attractive as they are orphan disorders in which drug development can be rapid. Similar strategies led to approved treatments such as lamotrigine for Lennox-Gastaut syndrome, vigabatrin for infantile spasms, and stiripentol for Dravet syndrome.[28]

Although many new medications were approved in the last 15 years, there is still a desperate unmet need. Treatment-resistant epilepsies impair quality of life and contribute to long-term cognitive and behavioral disorders. These patients often receive high doses of multi-AED regimens that cause significant side effects. Very few AEDs were carefully studied for long-term adverse effects. Therefore, it is understandable that patients, parents, and families would be interested in medical marijuana to treat epilepsy, particularly with increasing anecdotal reports of dramatic benefits. We believe a critical first step is systematical investigation of CBD, or other well-defined compounds or products as potential epilepsy therapies. Characterizing the safety and efficacy of marijuana products and their possible role in treating epilepsy in children and adults depends on gathering rigorous clinical experience and data from randomized placebo-controlled, double blind studies—whether of medicinal marijuana or single compounds such as CBD.

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The case for medical marijuana in epilepsy

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Summary

Charlotte, a little girl with *SCN1A*-confirmed Dravet syndrome, was recently featured in a special that aired on CNN. Through exhaustive personal research and assistance from a Colorado-based medical marijuana group (Realm of Caring), Charlotte's mother started adjunctive therapy with a high concentration cannabidiol/Δ^9-tetrahydrocannabinol (CBD:THC) strain of cannabis, now known as Charlotte's Web. This extract, slowly titrated over weeks and given in conjunction with her existing antiepileptic drug regimen, reduced Charlotte's seizure frequency from nearly 50 convulsive seizures per day to now 2–3 nocturnal convulsions per month. This effect has persisted for the last 20 months, and Charlotte has been successfully weaned from her other antiepileptic drugs. We briefly review some of the history, preclinical and clinical data, and controversies surrounding the use of medical marijuana for the treatment of epilepsy, and make a case that the desire to isolate and treat with pharmaceutical grade compounds from cannabis (specifically CBD) may be inferior to therapy with whole plant extracts. Much more needs to be learned about the mechanisms of antiepileptic activity of the phytocannabinoids and other constituents of *Cannabis sativa*.

KEY WORDS: Cannabidiol, CBD, THC, Medically refractory epilepsy, Dravet syndrome, Charlotte's Web.

Case Report: Charlotte Figi

Charlotte's first seizure was prolonged status epilepticus at 3 months of age. She had frequent bouts of febrile and afebrile status epilepticus as well as tonic, tonic–clonic, and myoclonic seizures. She quickly transitioned care to a Level 4 Epilepsy Center, and her epileptologist confirmed an *SCN1A* gene mutation, and diagnosed her with Dravet syndrome (DNA Variant I: transition C>T; Nucleotide position: 2791; Codon 931; Amino Acid Change: Arginine > Cysteine; Variant Type: disease associated mutation (heterozygous)/Athena Diagnostics, 2009). She began losing milestones, and by 5 years of age her family was told that she "had reached the end of the road," failing many medications (levetiracetam, oxcarbazepine, topiramate, zonisamide, valproate, clobazam, clonazepam, and valium) and the ketogenic diet. Charlotte had significant cognitive and motor delays, required a feeding tube for nutrition and water, struggled to walk and talk, and was full assist with her activities of daily living. At this point "Charlie" was experiencing up to 50 generalized tonic–clonic seizures per day.

A Mother's Account: Paige Figi

I had heard of a California parent successfully treating an epileptic child's seizure with cannabis, and because we live in Colorado, another state with legalized medical marijuana, I got busy doing research. I spoke with parents, doctors, scientists, chemists, marijuana activists, growers, medical marijuana patients, lawyers, and dispensary owners. The literature was confusing, with some papers suggesting that marijuana appeared to help seizures, and other papers suggesting that seizures got worse. What began to emerge, however, was interest in a less talked about component of

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marijuana, a phytocannabinoid called cannabidiol, or CBD. It appeared to have no psychotropic properties, and the animal studies suggested that it might be very effective against seizures.

Unfortunately, most people in the marijuana industry as well as physicians initially discouraged me from pursuing cannabis therapy, feeling that Charlotte was too much of a liability because she would be the youngest medical marijuana patient in the state at 5 years old. Eventually, I found Joel Stanley, who along with his brother had dedicated themselves to breeding a rare, high CBD strain of cannabis. After getting the green light from our team of epileptologists, pediatricians, and the reluctant state of Colorado, I started Charlotte at low doses of a sublingual preparation of the plant extract. I treated as I would with any antiepileptic drug, starting low and slowly increasing the extract dose, keeping the THC content sufficiently low to avoid psychotropic effects. For the first time since her seizures started, Charlotte experienced seven consecutive days without a single seizure! With a baseline frequency of 300+ convulsions (generalized tonic–clonic [GTC]) per week, by month three of high concentration CBD extract, Charlotte had a >90% reduction in GTC seizures, and had been weaned from her other antiepileptic drugs. Now at 20 months after starting what the Stanley Brothers would eventually dub "Charlotte's Web" (CW), Charlotte has only 2–3 nocturnal GTC seizures per month, is feeding and drinking orally and on her own, sleeps soundly through the night, and her autistic behaviors (self-injury, aggressiveness, self-stimulating behavior, poor eye contact, and poor social interaction) have improved. She has had only one episode of autonomic dysfunction associated with Dravet syndrome in the same time period. She is finally walking and talking again.

At first it was too good to be true, but her control was so much better that we began to wean her clobazam, which was the only medication she was taking at the time we started Charlotte's Web. By the end of the first month, she was entirely off clobazam and had only had 3 GTC seizures. Several months later we still could not believe that CW was working so well and started to slowly back down on the dose. When we reached 2 mg of CBD/lb per day (from her steady dose of 4 mg CBD/lb per day), Charlotte's seizures started coming back and when she was completely off the CW, her seizures returned to 5–10 GTC seizures per day for 3 days, at which time we restarted CW. To see if the seizures would recur without CW, we have done this two other times and have had the same results each time.

Based on Charlotte's success, the Stanley Brothers created a nonprofit organization to address the needs of other patients with catastrophic epilepsy syndromes by helping them gain access to consistent, high quality, lab-tested, high-CBD–content cannabis. They will have treated >200 patients by early 2014. Families are moving from across the country and internationally to Colorado for treatment with CW.

Controlling Convulsions with Cannabis

Cannabis sativa has a long history of medicinal use, with the earliest documentation around 4000 B.C. in China, for the treatment of rheumatism, pain, and convulsions. In fact, cannabis was available over-the-counter in U.S. pharmacies for a variety of maladies until 1941, following passage of the Marijuana Tax Act of 1937, which limited its access. Finally, the Controlled Substances Act of 1970 classified cannabis as Schedule I, making its use illegal. Although the political environment surrounding "pot" hindered prospective human clinical investigation, researchers continued to elucidate the structure and activity of *C. sativa*. Mechoulam et al.[1] determined the structure of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in 1963. A few case reports suggested anticonvulsant activity of Δ^9-THC, but psychotropic side effects were often rate limiting.[2,3] A conflicting report suggested that the smoking of marijuana may be proconvulsant.[4] In 1973, Carlini[5] first demonstrated the anticonvulsant effects of CBD, its absence of any clear toxicity, and its lack of psychotropic effects. In 1975, Juhn Wada protected cats[6] from kindled seizures with Δ^9-THC, and prevented seizures in already kindled baboons.[7] In 1980, Cunha et al.[8] performed a randomized, double-blind, placebo controlled trial of 15 patients who received either CBD or placebo, in addition to their existing medication. Four of the eight patients "remained almost free" of convulsions; three additional patients demonstrated "partial improvement," and one of eight had no effect at all. In contrast only one of the placebo patients showed improvement.

Part of the challenge of understanding why cannabis has apparently contradictory effects in epilepsy likely has to do with the complexity of the plant itself. *Cannabis sativa* has 489 known constituents,[9] only 70 of which are cannabinoids, with the remainder including potentially neuroactive substances such as terpenes, hydrocarbons, ketones, aldehydes, and other small hydrophobic compounds capable of crossing the blood–brain barrier. The variability of the strain-specific ratios of the most common cannabinoid, Δ^x-THC, and the second most common cannabinoid, CBD_x, offers further complexity in utilizing whole cannabis as an antiepileptic. In addition, the mode of administration likely affects bioavailability and neuroactivity. For instance, smoked and vaporized cannabis requires heat, which may alter the putative antiepileptic substance(s), whereas ingested cannabis must survive the acidic environment of the stomach and first pass metabolism. The extraction method is also critical, as the conditions and solvents used to separate these phytocompounds may alter them in the process.

The attractiveness of isolating a single compound that is responsible for a specific desired attribute is not lost on phy-

sicians, patients, parents, growers, and scientists, but it is as likely that a combination of neuroactive substances taken together rather than a single substance is responsible for any potential antiepileptic effect. For instance, the endocannabinoid system was discovered when the endogenous receptor for Δ^9-THC was identified in 1990.[10] The seven transmembrane G protein–coupled receptor called cannabinoid receptor type 1 (CB_1) mediates neuronal inhibition by promoting decreased calcium influx and increased potassium efflux. In 1992, the endogenous ligands to CB_1 were identified: "anandamide," an arachidonic acid derivative, and 2-arachidonoyl glycerol (2-AG), a phosphatidyl inositol precursor. These endocannabinoids are produced on demand during excessive neuronal excitation and are felt to be part of a natural dampening feedback loop. However, they have been found on both γ-aminobutyric acid (GABA)ergic as well as glutamatergic neurons, so their net effect is not entirely predictable. Although this may offer one possible mechanism by which cannabis controls seizures (or exacerbates them), cannabidiol does not bind to CB_1, and at this time its molecular target is not completely understood. CBD may be an agonist of 5-HT1a receptor, with similar affinity as serotonin,[11] or an agonist of a novel endocannabinoid receptor GPR55.[12] It is possible that CBD and Δ^9-THC work synergistically to suppress seizures. In fact Ethan Russo, senior medical advisor to GW Pharma, recently reviewed the evidence for the "entourage effect" of the phytocannabinoids and terpenoids,[13] and he makes a strong case for their synergistic effects in a variety of disease states.

Based on conversations with the parents who are currently pursuing Charlotte's Web, the most compelling arguments for the need to study whole cannabis therapy are the concept of autonomy and availability. A naturally occurring and potentially effective herbaceutical is very attractive to these families. Apart from the daily challenges and emotional toll of caring for children with a high frequency of convulsions and/or drop attacks, the risk of sudden unexplained death in epilepsy (SUDEP) looms over these caretakers. The present availability of a potentially useful therapy is driving a flurry of families to uproot and relocate to Colorado. Although the excitement surrounding Epidiolex (GW Pharma's pharmaceutical grade CBD plant extract) is high among these families, their access to the clinical trial sites seem even more remote than trying their luck in Colorado, and many are not willing to wait the countless years of pharmaceutical approval anticipated for Epidiolex, as their children's SUDEP risk continues to accumulate. The obvious and very serious problem is that patients and families may mistake what available science there is behind cannabis research and attempt to extract whole plant compounds on their own. Anecdotal accounts have surfaced locally since the story of Charlotte aired on CNN of severe pediatric intoxications resulting from stove-top extractions with butter. Other reports reveal that in the haste of moving, proper transition planning is ignored and many of these children are ending up in the intensive care unit in status epilepticus after their cross-country move. Also new since the airing of Charlotte's story, Colorado dispensaries are touting their own versions of "high CBD content" tinctures, ingestibles, and capsules. With little to no ability to keep up with the regulatory demands of the medical/recreational cannabis industry, quality control of available cannabis products is next to impossible at this time, but critically needed.

Despite all of the challenges of medical marijuana as a potential therapy for epilepsy, what is not controversial is the need for a call for calm, and at the same time a call for thoughtful and thorough pharmacologic and clinical investigation into cannabis and its many constituent compounds to confirm or disprove its safety and antiepileptic potential. Growers and regulators must satisfy concerns about consistency, quality, and safety before medical cannabis will ever gain legitimacy as a mainstream therapeutic option. Investigations involving children with catastrophic epilepsy syndromes require well-conceived double-blinded placebo protocols. Not only are many of these children "at the end of the road" of therapeutic options, but some families have invested heavily to move to states with legalized cannabis, and the intense desire for a successful therapy can impact clinical trial results.

As would be expected, well-intentioned and well-informed physicians, lawmakers, patients, and parents come down on different sides of the cannabis question, but in states that have chosen to legalize cannabis, failure to understand the intense desire of a large population of patients with epilepsy to use medical cannabis for the treatment of epilepsy[14] is foolish at best and dangerous at worst. In Colorado we are at "ground zero" for this debate, and it behooves us to educate the public, quiet the frenzy, and inform the proper design and execution of clinical research that will answer the question of whether high concentration CBD cannabis is an effective antiepileptic agent.

Disclosure or Conflict of Interest

None of the authors has any conflict of interest to disclose. Furthermore, Dr. Maa wishes to explicitly state that he does not have a treatment relationship with Charlotte Figi, and as faculty at University of Colorado and Denver Health and Hospitals does not provide prescriptions for medical marijuana or sign for Colorado State Medical Marijuana Registrations. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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