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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