# 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*—$\Delta^9$-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, $\Delta^9$-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 $\Delta^9$-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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