Cannabidiol for Epilepsy: New Hope on the Horizon?

Paul E. Sanmartin, MD and Kamil Detyniecki, MD

Comprehensive Epilepsy Center, Department of Neurology, Yale University, New Haven, Connecticut

ABSTRACT

Epilepsy is a common neurologic disorder; it is estimated that ~50 million people are affected worldwide. About one third of those patients are drug resistant, defined as failure to stop all seizures despite adequate trials of at least 2 appropriate medications. There has been an enormous interest in developing antiepileptic drugs with novel mechanisms of action. This review discusses the evidence supporting the anticonvulsant properties of cannabis in humans, focusing on cannabidiol. We begin by exploring the early and somewhat anecdotal evidence that was recently replaced by high-quality data from randomized controlled studies, which subsequently led to the US Food and Drug Administration approval of a purified cannabidiol extract for the treatment of 2 highly refractory pediatric epilepsy syndromes (Dravet and Lennox-Gastaut). (*Clin Ther*. 2018;■:1–4)

Key words: cannabis, cannabidiol, marijuana, epilepsy, seizures.

For >4000 years, the cannabis plant has been used for several medical conditions, ranging from eating disorders and rheumatism to chronic pain and convulsions.[1] However, high-quality evidence to support the therapeutic use of the cannabis plant in epilepsy was lacking because, until recently, most available evidence was anecdotal. In the 19th century, 2 prominent English neurologists, Reynolds and Gowers, mentioned that cannabis may aide in treating seizures.[2] The 2 most well-characterized active constituents of cannabis are tetrahydrocannabinol (THC), which has psychoactive, anticonvulsant, and pro-convulsant effects (among many others), and cannabidiol (CBD). CBD is the main focus of the present article, given its predominantly anticonvulsive effects.

Epilepsy is one of the most common neurologic disorders; it has been estimated that at least 50 million people worldwide are affected with this disease.[3] Epilepsy has devastating effects on patients' lives, both as a result of the physical sequelae as well as the vast socioeconomic consequences. The World Health Organization's 2010 Global Burden of Disease study ranked epilepsy as the second most burdensome neurologic disorder worldwide in terms of disability-adjusted life years.[3,4] Unfortunately, ~30% of patients do not achieve remission despite appropriate therapy with antiepileptic drugs,[5] which prompts patients and their loved ones to seek alternative therapies and new treatments.

Over the last 3 decades, significant advances have been made in understanding the pharmacology and mechanism of action of cannabinoids. The 2 main biologically active cannabinoids that have been studied the most are THC and CBD.[6,7] In animal models, THC has primarily anticonvulsant properties but is pro-convulsant in some species[8]; CBD is more consistently anticonvulsant.[9] THC is a partial agonist at cannabinoid type 1 (CB1) receptors, which are mostly located in the brain in the inhibitory (GABA)ergic and excitatory glutamatergic neurons.[10] CBD is the major nonpsychoactive compound and can diminish the effects of CB1 activation. Although its anticonvulsant properties are not fully understood, it seems that its effects are independent of the CB1 receptors and follow a bell-shaped dose–response curve.[11,12]

There is a growing interest in medical cannabis, and CBD in particular, as a novel treatment for poorly controlled epilepsy. This topic recently regained importance after media reports began highlighting the almost miraculous response of previous intractable pediatric cases to CBD-rich cannabis extracts. In 2013, CNN reported the case of Charlotte Figi,[13] who suffered from a highly intractable pediatric epilepsy syndrome (Dravet). She reportedly was having >300 convulsions weekly; after the administration of high CBD-content cannabis, her seizure frequency was reduced to 2 to 3 convulsions per month. In the same year, Porter and

Accepted for publication July 26, 2018.
https://doi.org/10.1016/j.clinthera.2018.07.020
0149-2918/$ - see front matter

Jacobson conducted an Internet-based survey in which 84% of parents who had administered CBD-enriched cannabis extract to 19 children with intractable epilepsy reported an important reduction in seizure frequency.[14] In 2015, Hussain et al[15] conducted a survey with similar results. However, the lack of placebo control subjects and unblinded self-assessment of efficacy and tolerability are a major confounding for those reports, and neither the doses nor the exact composition of the different cannabis extracts could be determined.

In December 2015, Devinsky et al[16] presented the first large-scale prospective multicenter study examining the use of CBD in epilepsy. In this study, patients were orally administered a purified 98% oil-based CBD extract (Epidiolex® [GW Pharmaceuticals plc, Cambridge, United Kingdom), and the dose was uptitrated depending on tolerance. A total of 214 patients with Dravet syndrome, Lennox-Gastaut syndrome, and other intractable pediatric epilepsies were enrolled, and both seizure frequency and side effects were monitored for a minimum of 12 weeks. Results showed a median reduction in monthly seizures of 36.5%. Although side effects were frequently reported (128 [79%] of the 162 patients within the safety group), the majority were mild and rarely led to discontinuation of the drug. The main limitations of this study were the open-label, observational nature; the short follow-up time (12 weeks); the lack of a control group; and the drug interactions that could have potentially overestimated the efficacy results. CBD is a potent inhibitor of cytochrome P450 3A4 and cytochrome P450 2C1; it has the potential to increase serum concentrations of background antiepileptic drugs and their active metabolites, which could account for its efficacy and side effects.[17,18] A small study (25 patients) published in 2015 showed an increase in clobazam levels with CBD. In this study, 9 of 13 subjects who were taking clobazam had a >50% decrease in seizures.[19,20]

In January 2016, a retrospective Israeli study describing the effect of CBD-enriched medical cannabis on children with epilepsy was published.[21] In this study, 74 patients with intractable epilepsy were enrolled and started on cannabis oil extract, and they continued it for at least 3 months (average, 6 months). The selected formula contained CBD and THC at a ratio of 20:1 in olive oil. Seizure frequency was assessed according to parental report during clinic visits. The results showed a reduction in seizure frequency in 89% of all children enrolled, with improvement in behavior and alertness, language, communication, motor skills, and sleep. However, the study had several limitations, including the lack of a control group, no consistent rate of dose elevation, reliance upon parental report for seizure frequency, short duration of the study, lack of a long-term outcome, and lack of measurement of other drug levels.

In May 2017, a double-blind, placebo-controlled trial by Devinsky et al[22] was published in the *New England Journal of Medicine*. A total of 120 patients with Dravet syndrome were randomly assigned to receive either a purified CBD oral solution (Epidiolex) at a dose of 20 mg/kg per day or placebo, in addition to their standard antiepileptic treatment. Selected patients were children and young adults aged 2 to 18 years whose seizures were not controlled with their current antiepileptic drug regimen. The primary end point was the change in convulsive seizure frequency over a 14-week period. In this study, the median frequency of convulsive seizures per month decreased from 12.4 to 5.9 in the CBD arm compared with a decrease from 14.9 to 14.1 with placebo. The percentage of patients who had at least a 50% reduction in convulsive seizure frequency was 43% with CBD and 27% with placebo. The percentage of patients who became seizure-free was 5% with CBD and 0% with placebo. Side effects were common and usually mild to moderate, which is consistent with the previous open-label studies.

Finally, in March 2018, a randomized, double-blind, placebo-controlled trial was conducted at 24 clinical sites in the United States, the Netherlands, and Poland.[23] The goal of this study was to investigate the add-on effect of a purified CBD (Epidiolex) for drop seizures in 171 patients with treatment-resistant Lennox-Gastaut syndrome. Patients were randomized to receive either CBD daily or placebo for 14 weeks. The study reported a reduction in monthly drop seizures of 43.9% in the CBD group versus 21.8% in the placebo group. The reported side effects were minor and similar to previously described studies. This trial is the first randomized study designed to assess the efficacy and safety of CBD as an add-on anticonvulsant therapy for patients with Lennox-Gastaut syndrome which showed that even in this treatment-resistant population, statistical and clinical improvements in seizure frequency occurred when CBD was added to other antiepileptic drug regimens. Some limitations included