Journal of Epileptology • 2019 • 27 • 10.2478/joepi-2019-0004

Cannabinoids in the treatment of epilepsy – an updated review

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Received June 5, 2019
Accepted for publication on-line August 20, 2019
Published on-line September 5, 2019

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SUMMARY

Introduction. It is estimated that 30% of people with epilepsy continue to have seizures despite treatment. The approval of many new antiseizure drugs during the past two decades has not substantially reduced the proportion of patients with medically refractory disease. Patients need new treatments. Many families choose to try alternative therapy options. An abundance of preclinical evidence and anecdotal human data support the use of cannabinoids in the treatment of epilepsy.

Aim. The present review paper aims to present the current state of knowledge regarding the effectiveness and safety of cannabinoids in the treatment of epilepsy.

Material and methods. This review covers the most relevant and recent papers identified using the PubMed database.

Results and discussion. Cannabidiol has shown anticonvulsant activity in many acute animal models of seizures. Recently three well controlled randomized trails focused on the potential usefulness of cannabinoids in the treatment of epilepsy have been published. Based on these publications, the US Food and Drug Administration approved in 2018 a purified, plant-derived cannabinoid for the treatment of seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome.

Conclusion. An abundance of preclinical evidence and anecdotal human data support the use of cannabinoids in the treatment of epilepsy. Recently purified, plant-derived cannabinoid was approved for the treatment of seizures in patients with Dravet syndrome and Lennox-Gastaut. Additional data are needed to determine the long-term efficacy and safety of cannabidiol for severe epilepsy syndromes

Key words: cannabinoids • epilepsy • treatment

INTRODUCTION

Epilepsy is one of the most common disorders of the nervous system. It is a health problem as well as a social and economic one. Epilepsy affects over 65 million people worldwide (CDC, 2012). Patients who suffer from seizures in spite of the administration of two subsequent, appropriately-selected antiepileptic drugs (AEDs) that are well applied and tolerated, are diagnosed with refractory epilepsy (Kwan et al., 2010). It is estimated that 30% of people with epilepsy continue to have seizures despite treatment (Brodie et al., 2012; Kwan, Brodie, 2000). The approval of many new antiseizure drugs during the past two decades has not substantially reduced the proportion of patients with medically refractory disease (Brodie et al., 2012). The safety and side-effect profile of antiseizure drugs has improved, but side effects related to the central nervous system are common and affect quality of life (Perucca, Gilliam, 2012). Patients need new treatments that control seizures and have fewer side effects. Many families choose to try non-pharmaceutical or alternative therapy options. Cannabis-based treatment for epilepsy has recently received prominent attention in the lay press

and in social media. The reports of dramatic improvements in seizure control in children with severe epilepsy have been published (Gupta, 2013). An abundance of preclinical evidence and anecdotal human data support the use of cannabinoids in the treatment of epilepsy.

AIM

The present review paper aims to present the current state of knowledge regarding the effectiveness and safety of cannabinoids in the treatment of epilepsy in humans.

MATERIAL AND METHOD

This review covers the most relevant recent papers identified using the PubMed database. The search was conducted in June 2019 and included the terms: cannabinoids, epilepsy, treatment, cannabidiol (CBD), tetrahydrocannabinol (THC) It encompasses articles published in English from 2010 to 2019. Randomized controlled trails and reviews was included. Other types of studies were excluded. Also, additional relevant publications were identified within the various references highlighted within the original papers.

RESULTS AND DISCUSSION

THC and CBD

Cannabis has been used by humanity in a variety of medical settings via a range of different formulations for more than 5000 years. The plant *Cannabis sativa*, commonly known as marijuana, is composed of more than 500 compounds and new components continue to be discovered (Radwan et al., 2009). Although there are many preparations with cannabinoids only some of them are being investigated and developed as anticonvulsants. These biologically active compounds isolated from the cannabis plant are termed phytocannabinoids. The best studied of these are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) and their metabolites. More recently, trials have begun with Cannabidivarin (CBDV). CBDV has similar molecular structure to CBD but instead of having a pentyl chain, it has a propyl chain. This propyl cannabinoid has slightly different properties than CBD. CBD was isolated in 1940 and its structure was elucidated in 1963, whereas THC was isolated and characterized in 1964 (Mechoulam, Shvo, 1963). In the late 1980s it was found that THC canbind to two G-protein-coupled cell membrane receptors, consequently named the cannabinoid type 1 (CB1) and type 2 (CB2) receptors, to exert its effects. The discovery of cannabinoid receptors in the CNS led to a search for endogenous substances interacting with these receptors. These endogenous counterparts of phytocannabinoids, are known as endocannabinoids. The most important of which are the arachidonic acid derivatives anandamide (2-arachidonoylethanolamide) and 2-arachidonoyl glycerol (Reddy, Golub 2016). These endocannabinoids are produced on demand during excessive neuronal excitation. Despite overt differences in their chemical structures, phytocannabinoids share three-dimensional aspects of their structure with endocannabinoids (Maccarrone et al., 2017; Chiurchiu et al., 2018). This resemblance is the reason why phytocannabinoids can bind the same targets that are recognised by endocannabinoids. Phytocannabinoids, unlike the endocannabinoids, have terpenophenolic structures because they cannot be synthesised nor hydrolysed by the body. It is important because the biological activity of endocannabinoids is tightly regulated through metabolic control (Iannotti et al., 2016; Maccarrone et al., 2015). THC possible use as an antiepileptic drug (AED) in humans has been hindered by its known psychotropic effects. CBD and CBDV are lacking these complicating properties (Rosenberg et al., 2015). Unlike THC, CBD does not activate CB1 and CB2 receptors. However, CBD interacts with many other, non-endocannabinoid signaling systems. It is a called "multitarget" drug (Devinsky et al., 2014). The plausible and implausible CBD's molecular targets as well as the potential pharmacological effects of CBD in neurological disorders including epilepsy has been reviewed elsewhere (Ibeas Bih et al., 2015). It is believed that its anticonvulsant action of cannabidiol is associated with at least some of the following mechanisms: stimulation of 5-HT1a receptors, inhibition of glutamate release, inhibition of noradrenaline, dopamine and adenosine reuptake, stimulation of glycine receptors and stimulation and desensitization of transient receptor potential class channels (ankyrin and vanilloid types, i.e. TRPA1, TRPV1 and TRPV2 receptors) (Leo et al., 2016). Anticonvulsant effect of CBDV is, similar as CBD, probably related to its agonistic action on TRPA1, TRPV1 and TRPV2, while its inhibitory action on diacylglycerol lipase-α, which synthesizes 2-arachidonoylglycerol, an endocannabinoid, remain yet to be connected to anticonvulsant properties (Hill et al., 2013; Iannotti et al., 2014).

Preclinical data and anecdotal reports

In the late 19th century, prominent English neurologists including Reynolds (Reynolds, 1861) and Gowers (Gowers, 1881) used cannabis to treat epilepsy. However, the use of cannabis for epilepsy remained very limited, and despite anecdotal successes, cannabis received scant or no mention from English language epilepsy texts in the late 19th and early to mid-20th centuries. Some anecdotal reports suggest that cannabis has antiepileptic properties and would be effective to manage focal epilepsies and generalized tonic-clonic seizures, however, also seizure exacerbation after cannabis use has been observed (Detyniecki, Hirsch, 2016).

The two cannabinoids that have been mostly used in treating epilepsy are THC and CBD. Many early studies focused on THC. The results of these studies demonstrated mixed efficacy in acute seizure models in various species (Andrew et al., 2013). In some models, THC reduced seizure frequency or severity, whereas in other studies there was no effect. Even in some naive, seizure-susceptible rats and rabbits, THC actually provoked epileptiform activity (Stadnicki et al., 1974; Martin, Consroe, 1976). These findings suggest that activation of CB1 receptors is unlikely to yield therapeutic benefit for patients with epilepsy (Devinsky et al., 2014). As highlighted earlier, the use of THC was limited due to its known psychotropic effects. CBD has shown anticonvulsant activity in many acute animal models of seizures, whereas few data and no data are present respectively in animal models of chronic epilepsy and as well as in animal models of epileptogenesis (Devinsky et al., 2014; Santos et al., 2015). In these preclinical experimental studies, CBD has been effective similarly to the AEDs used in clinical therapy (Scuderi et al., 2009). However, CBD mechanisms of action are complex and as yet not entirely clear. Trials with CBDV are still underway.

Safety

Much of the available data regarding the safety and side-effect profile of cannabinoids, especially with long-term use, come from studies examining the effects of recreational use (Hall, Solowij, 1998; Volkow et al., 2014). The endocannabinoid system undergoes development in childhood and adolescence. Long-term exposure to marijuana may lead to cognitive and behavioral changes. In long-term adult users imaging studies of the brain revealed altered structure and function of the prefrontal cortices and precuneus (Volkow et al., 2014) and decreased volume in the hippocampi and amygdalae (Lorenzetti et al., 2015). Until more data become available, the neurodevelopmental risks of cannabinoid-based therapies should be weighed against the potential benefits for seizure control. Long-term recreational use of cannabis is associated with a risk of dependence, but little is known regarding the potential for the abuse of cannabinoid-based treatments when they are used in a clinical practice (Volkow et al., 2014). Some safety concerns have been raised with regard to the pharmacokinetic interactions of cannabinoids in patients with epilepsy who are long-term users. Cannabinoids can inhibit cytochrome P-450 (CYP) enzymes which help to metabolize many AEDs (Patsalos, Perucca, 2003). This inhibition can potentiate drug efficacy and toxicity. CBD is metabolized through the P-450 system and is a potent inhibitor of CYP2C9, CYP3A4 and CYP2C19 (Stout, Cimino 2014; Zendulka et al., 2016). The situation with CBDV is still unclear, although a similar adverse pharmacokinetic scenario is likely.

These isoenzymes are induced by AEDs, such as carbamazepine, topiramate, and phenytoin, and are inhibited by others, such as valproate (Patsalos, Perucca, 2003). The potential for drug-drug interactions between antiseizure drugs and cannabinoids may be bidirectional. It was shown that cannabidiol can raise the serum levels of the N-desmethyl metabolite of clobazam, which can have antiseizure and sedative effects. (Friedman et al., 2014). This interaction is likely to be clinically important since patients prescribed clobazam are more likely to experience sedation with cannabidiol than those not taking clobazam (Devinsky et al., 2015). The antiseizure effect of CBDV is similar to CBD not mediated by CB1 receptors and both these molecules possibly have other unique mechanisms of action (Iannotti et al., 2014).

Patient's belief and scientific evidence

Another obstacle to scientific inquiry into cannabinoids for the treatment of epilepsy is the perception among many patients and caregivers that sufficient evidence of their safety and efficacy already exists (Mathern et al., 2015). The gap between patient beliefs and available scientific evidence highlights a set of factors that confound cannabinoid research and therapy. One of them is the naturalistic fallacy. It is the belief that nature's products are safe. Other gaps are the conversion of anecdotes and strong beliefs into facts and failure to appreciate the difference between research and treat-

ment (Henderson et al., 2007). It is worthy to mention one study of children with epilepsy in Colorado (Press et al., 2015). In this trial the rate of response to therapy reported by parents who had moved their family to the state to receive cannabinoid therapy was more than twice as high as that reported by parents who were already residing in the state (47% vs 22%) (Press et al., 2015). This finding suggests that the stronger the belief that the drug will be beneficial and the greater the sacrifice involved to obtain the drug, the greater the reported response.

Placebo response rates are high among children and adolescents with a wide variety of conditions (Weimer et al., 2013) The issue of high response rates to placebos in studies of children is especially relevant to epilepsy and emphasizes the importance of placebo-controlled trials. According to results of metaanalysis performed among patients with treatment-resistant focal epilepsy, children had more improvement with placebo than did adults (19.9% vs 9.9%), although there was no significant difference in the response to active treatment (Rheims et al., 2008). Moreover, children with intellectual disability and severe epilepsy are especially prone to elevated response rates to placebo. It should be emphasized that contrary to belief of some patients and their caregivers the efficacy in treatment of epilepsy was proved only for purified, plant-derived cannabinoid, named cannabidiol (FDA, 2018). Unfortunately, different marijuana strains have varying amounts of THC and CBD. The improvement after the introduction of CBD extracts followed by seizure worsening in two children with treatment-resistant epilepsy after a short time with associated signs of toxicity from THC has been recently described (Crippa et al., 2016). In both children, a rapid improvement symptom of toxicity with seizure remission in both of children occurred when purified CBD replaced the extract with no THC. The pharmacological potency of THC is much higher than that of CBD, and it can produce toxicity in a much smaller dose. This highlighted the need for well-standardized formulations with fixed high CBD and low THC concentrations for the treatment of epilepsy. Patients and their caregivers should be aware of using cannabinoids from unknown sources. Marijuana used for recreational purposes may not only be not effective but even dangerous in patients with epilepsy.

Results of controlled studies

To-date only two of the investigational cannabinoids were tested in clinical trials on patients with epilepsy; cannabidiol and cannabidivarin (Bialer et al., 2017). In the 1970s and 1980s four placebo-controlled studies of the use of cannabinoids for the treatment of epilepsy have been undertaken (Ames, Cridland, 1985; Cunha et al., 1980; Mechoulam, Carlini, 1978; Trembly, Sherman, 1990). In the first one, 15 patients with temporal lobe epilepsy and secondary generalized seizures, not well controlled by standard AEDs, were enrolled and randomized in groups treated in addition to their habitual AED therapy with CBD (200–300 mg per day, per os) or placebo. Study duration was 4.5 months. Of the 8 CBD treated patients, four became and remained seizure-free during the treatment with CBD (8–18 weeks), three exhibited a clinical improvement, while the other CBD treated patients did not improve. In the placebo group, 6 out of 7 patients remained unchanged and one has shown a clinical improvement. Drowsiness was reported by 4 patients on CBD. No severe side effects were reported (Cunha et al., 1980). In the second study, 12 patients with uncontrolled seizures and intellectual disability were divided in two groups treated with three capsules of sunflower oil (as placebo) or three capsules of sunflower oil and 100 mg of CBD for the first week. During the following three weeks, patients received two capsules per day. No differences in seizure frequency between the two groups were found. The only side effect was mild drowsiness (Ames, Cridland, 1985). In the third study, 9 patients with uncontrolled epilepsy in addition to their habitual AED therapy were treated with 200 mg daily of CBD or placebo. Study duration was three months. Two of 4 patients treated with CBD achieved seizure freedom, during the three months of treatment; one had only partial improvement, whereas the last one had not shown beneficial clinical effects. None of the patients treated with placebo had clinical improvement. No side effects were detected (Mechoulam, Carlini, 1978). The fourth trial was only presented at a conference. In this study, 12 patients were treated with a single-blind placebo for 6 months followed by double-blind 300 mg of CBD or placebo in a cross-over trial design. No statistics were performed. According to preliminary data analysis there was some reduction in seizure frequency (Trembly, Sherman, 1990). All four studies were considerably underpowered and had methodologic problems, including the small sample size and lack of blinding. All these results were summarized in a Cochrane review which concluded that "no reliable conclusions can be drawn at present regarding the effi-

cacy of cannabinoids as a treatment for epilepsy" (Gloss, Vickrey, 2014). This assessment was confirmed in a systematic review by the American Academy of Neurology (Koppel et al., 2014). Physicians have to be "evidence based" which entails undertaking randomized, double-blinded, placebo-controlled clinical trials (RCT). It is imperative that studies are blinded and well designed.

Recently three well controlled randomized trials focused on the potential usefulness of cannabinoids in the treatment of epilepsy have been published (Devinsky et al., 2015; Devinsky et al., 2017; Devinsky et al., 2018; Thiele et al., 2018). The first completed trial evaluated the efficacy of a purified oral CBD solution in 214 patients with severe, intractable, childhood-onset treatment resistant epilepsy. The aim of this open labeled study was to establish whether the addition of cannabidiol to existing AED regimens would be safe, well tolerated, and efficacious in children and young adults with treatment-resistant epilepsy. The primary endpoint was to establish the safety and tolerability of cannabidiol (administered orally and starting from 2–5 mg/kg and up-titrated to 25–50 mg/kg per day), and the primary efficacy outcome was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. The median change in monthly motor seizures from baseline was –36.5% (IQR – 64.70 to 0). The adverse event profile of cannabidiol was favorable, with mAEDs. Common adverse events included somnolence, diarrhea, fatigue, and decreased appetite. Only 5 of 162 patients stopping treatment because of an adverse event. The results of this trial suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy (Devinsky et al., 2015).

A subsequent trial enrolled 120 children with Dravet syndrome, aged 2–18 years, who experienced four or more convulsive seizures per month despite receiving one or more AEDs. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. Patients treated with cannabidiol (administered orally in daily doses up to 20 mg/kg per day), had a significantly greater reduction in seizures per month (12.4 seizures at baseline to 5.9 seizures) then in placebo group (14.9 seizures at baseline to 14.1 seizures). The adverse-event profile of cannabidiol in this trial was similar to that in the previous open-label trial (Devinsky et al., 2015). This trial showed that cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo among children and young adults with drug-resistant Dravet syndrome (Devinsky et al., 2017).

There have been two trials enrolling patients with Lennox-Gastaut syndrome (Thiele et al., 2018; Devinsky et al., 2018). The first randomized, double-blind trial to assess the efficacy and safety of cannabidiol (administered orally in 20 mg/kg daily dose) as add-on anticonvulsant therapy for patients with Lennox-Gastaut syndrome was the GWPCARE4 study. Patients in this study were highly treatment resistant. At baseline they had a median 73.8 drop seizures every 28 days despite current treatment with three or more concomitant AEDs. Even in this highly treatment-resistant population, statistically significant and clinically meaningful improvements in seizure frequency were observed following the addition of cannabidiol to existing AED regimens compared with placebo. Patients treated with cannabidiol had a significantly greater reduction in seizures per month (74.8 seizures at baseline to 31.4 seizures) then in placebo group (74.7 seizures at baseline to 5.3 seizures). In the cannabidiol group, the monthly frequency of drop seizures decrease was greater than in the placebo group. The observed tolerability profile for cannabidiol was consistent with that reported in a previous open-label trials (Devinsky et al., 2015). In this trial, a 20 mg/kg daily dose of cannabidiol as add-on therapy to existing AEDs significantly reduced the frequency of drop, non-drop, and total seizures in highly treatment-resistant patients with Lennox-Gastaut syndrome (Thiele et al., 2018). The results of this trial were replicated in a further trial comprising children and adults with the Lennox–Gastaut syndrome. In this study the addition of cannabidiol at a dose of 10 mg or 20 mg per kilogram per day to a conventional AED regimen resulted in greater reductions in the frequency of drop seizures compared to placebo (Devinsky et al., 2018). On the basis of above highlighted trials, the US Food and Drug Administration (FDA) approved in 2018 a purified, plant-derived cannabinoid, named cannabidiol, for the treatment of seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome (FDA, 2018).

Despite positive results in these two severe epilepsy syndromes, further studies are needed to determine if the anti-seizure effects of cannabidiol extend to other forms of epilepsy. Such trials are currently ongoing. Cannabidivarin is currently being tested in two phase II clinical trials aimed to evaluate its pharmacokinetics,

safety and tolerability compared to placebo, as add-on therapy in patients (aged 18–65 years) with inadequately controlled focal seizures. The studies are completed but results are not published yet. The studies are registered at Clinicaltrials.gov (available at: https://clinicaltrials.gov/ct2/show/NCT02369471 and https://clinicaltrials.gov/ct2/show/NCT02365610).

CONCLUSION

An abundance of preclinical evidence and anecdotal human data support the use of cannabinoids in the treatment of epilepsy. Recently purified, plant-derived cannabinoid, named cannabidiol was approved for the treatment of seizures in patients with Dravet syndrome and Lennox-Gastaut. The adverse event profile of cannabidiol is favorable, with most patients tolerating the drug well. The mechanism of antiepileptic action of cannabinoids in epilepsy is not exactly known and should be elucidated in the future. In addition, it is not known how to produce a formulation with consistent pharmacokinetics suitable for a major clinical trial program; it is not know whether cannabinoids will make a major difference in the lives of most people with pharmacoresistant epilepsy and those who care for them; it is not known why a few patients appear to have a miraculous response to cannabis derivatives. Is there a genetic reason for this? (Brodie, Ben-Menachem, 2018). Additional data are needed to determine the long-term efficacy and safety of cannabidiol for severe epilepsy syndromes (Devinsky et al., 2015; Devinsky et al., 2017).

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