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Chapter 11

Cannabis for Pediatric and Adult Epilepsy

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http://dx.doi.org/10.5772/intechopen.85719

Abstract

Epilepsy is a chronic disease of the central nervous system characterized by recurrent unprovoked seizures. Up to 30% of patients continue to have seizures despite treatment with appropriate anticonvulsant medications. The presence of abnormal oscillatory events within neural networks is a major feature of epileptogenesis. The endocannabinoid system can modulate these oscillatory events and alter neuronal activity making the phytocannabinoids found in *Cannabis* a potential therapeutic option for patients with treatment resistant epilepsy. Many in vitro and in vivo studies have demonstrated the anticonvulsant effects of several phytocannabinoids including Δ^9-tetrahydrocannabinol (Δ^9-THC) and Cannabidiol (CBD). Several small observational studies demonstrated a favorable response to cannabis herbal extracts (CHE) containing high concentrations of CBD in children with treatment resistant epilepsy. Two large double blinded clinical trials assessing the efficacy of pharmaceutical grade CBD have also been performed in children with treatment resistant seizures in Dravet syndrome and Lennox-Gastaut syndrome. Both studies demonstrated an improvement in seizure reduction in children taking CBD as compared to the placebo groups. To date there is very limited data regarding the use of cannabis based products to treat adult patients with treatment resistant epilepsy with only one randomized double blinded placebo controlled clinical trial underway.

Keywords: epilepsy, endocannabinoid system, cannabis, tetrhydrocannabinol, cannabidiol

1. Introduction

Recently, there has been renewed interest in the use of cannabis in patients with treatment resistant epilepsy. This has, in large part, been driven by a public perception that cannabis offers a safe and natural alternative to conventional anticonvulsant therapies. However, the

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phytocannabinoids found in the cannabis plant do offer some very unique anticonvulsant pharmacological properties that warrant further exploration.

In this chapter the authors will provide a brief review of epilepsy and epileptogenesis followed by a review of how the endocannabinoid system can alter the processes involved in the propagation and suppression of epileptic seizures. This is then followed by a review of the phytocannabinoids and their anticonvulsant mechanisms of action. Finally, the authors provide a historical background on the use of cannabis to treat patients with epilepsy and a review of the most recent clinical trials.

2. Epilepsy

Epilepsy is a chronic disease characterized by recurrent unprovoked seizures. It is defined as a disease of the brain in which the patient has either (1) two or more unprovoked seizures occurring more than 24 hours apart or (2) one unprovoked seizure and a probability of further seizures to be greater than 60% [1]. The prevalence of epilepsy worldwide is estimated to be between 4 and 10/1000 people with epilepsy accounting for up to 0.5% of the global burden of disease [2, 3]. There is significant geographic variation with prevalence rates of epilepsy prevalence rates being much higher in the developing world [4].

Most children and adults with epilepsy respond well to anticonvulsant therapy with approximately 50% of adults and 70% of children becoming seizure free with their first anticonvulsant medication [5, 6, 7]. Up to 30% of patients with epilepsy can be considered to be drug resistant which is defined by the International League Against Epilepsy as having failed two or more appropriate anticonvulsant treatments at an appropriate dosage [8, 9].

In patients who have failed two appropriate anticonvulsants the likelihood of seizure freedom with the addition of further anticonvulsant therapies is low. Treatment options for patients with drug resistant epilepsy include further trials of anticonvulsants, resective surgery, neural pathway stimulation with receptive or vagal nerve stimulation and dietary therapies [10]. Further trials of anticonvulsants in adults will result in 16% of patients who had failed their first two medications becoming seizure free [11]. In pediatric patients while the likelihood of achieving remission for 1 year or more with further medication trials is higher at 57%, many will continue to have relapses over time [12]. Resective surgery success rates (as defined as obtaining Engel Class 1 seizure freedom) in pediatric and adult patients with surgically amenable epileptogenic lesions range from 34 to 90% depending on the nature and extent of the lesion [10, 13].

A full review of the processes that result in brain abnormalities causing seizures (epileptogenesis) is beyond the scope of this chapter. However, in order to understand how cannabinoids can have potential in treating epilepsy it is worth knowing the basic principles of these processes. One of the major hallmarks of epilepsy is the presence of abnormal oscillatory events within neuronal networks in the form of recurrent interictal spikes and high frequency oscillations within the epileptic zones of the patients' brain [14]. These abnormal oscillations then

result in excessive synchronous firing of neurons causing an epileptic seizure with alteration in the patient's behavior, motor activity or sensorium. Epilepsy can result from injury (either ischemic or traumatic) to cortical brain structures or genetic, inflammatory, structural and metabolic disturbances within the brain. The main components of the development of the abnormal oscillations within neuronal networks and epileptogenesis (seizure development) are (a) neuronal hyperexcitability—the ability of neurons to generate abnormal intrinsic burst discharges (b) a loss of GABA mediated interneuron neuronal inhibition that would normally prevent these discharges from spreading to adjacent neurons and (c) neuronal hypersynchrony in which excessive synaptic enhancement of neighboring neurons through the development of excitatory pathways allows these bursts to spread in a synchronous manner within a group of neurons [15]. Neuronal hyperexcitability can arise from abnormalities in excitatory or inhibitory neurotransmitter receptors resulting in a loss of the normal balance between neuronal excitation and inhibition. Of particular interest in epileptogenesis are the excitatory glutamatergic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors [16]. Alterations in ion channel function as is seen in the channelopathy associated epilepsies such as Dravet syndrome also lead to neuronal hyperexcitability [17].

3. The endocannabinoid system and epilepsy

The endocannabinoid system comprises the two endogenous endocannabinoid receptors (CB1R and CB2R) their two endogenously produced endocannabinoids; anandamide (*N*-arachidonyl-ethanolamide) and 2-AG (2-arachadonoylglycerol) which act as endogenous CBR ligands as well as the enzymes involved in endocannabinoid production and breakdown. Of the endocannabinoids produced in the human brain, 2-AG is produced in much higher concentrations and plays the most significant role in regulation of oscillatory networks [18]. For a full review of the endocannabinoid system please refer to this book's introduction and the review article by Ligresti et al. [19] CB1R is one of the most abundant G protein-coupled receptors (GPCR) within the mammalian brain and is expressed on the presynaptic axon terminal. In response to activation of the postsynaptic neuron, anandamide (a partial CB1R agonist) and 2-AG (a full CB1R agonist) are both produced within and released by the postsynaptic neuron. Activation of the presynaptic CB1R receptors by the endocannabinoids then results in a temporary suppression in voltage gated Ca^{2+} channels and activation of K^{+} channels resulting in suppression of further neurotransmitter release from the presynaptic neuron [20].

Although CB1R is one of the most abundantly expressed GPCRs in the brain, its expression is concentrated within certain groups of neurons. For example, in the hippocampus, CB1R expression is concentrated on the axon terminals of inhibitory GABAergic CA1 region interneurons and Schaffer collaterals arising from CA3 pyramidal cells [22]. These interneurons play a key role in the formation and maintenance of normal oscillatory behavior in the hippocampus essential for memory formation [18]. The effect of stimulation of CB1R is very localized within neuronal networks both from a spatial and temporal point of view. This

is achieved by the production of monoacylglycerol lipase (MAGL) by astrocytes and nerve terminals which breaks down 2-AG in the synaptic cleft. This temporal and spatial control allows for precise regulation of oscillations within neuronal networks by the endocannabinoid system [18].

During an epileptic seizure there is excessive glutamate release from presynaptic excitatory neurons. In rodent models of epilepsy this has been shown to cause increased production of both 2-AG and anandamide that in turn active CB1R on the glutamatergic axon terminals to decrease the release of further excessive glutamate. This prevents further neuronal hyperexcitability which may play a role in terminating seizures. The increased anandamide is felt to play a role in preventing seizure induced excitatory neurotoxic effects [18, 21].

Temporal lobe epilepsy secondary to mesial temporal sclerosis (scarring of the hippocampi) is a common cause of epilepsy in adults that is often amenable to surgical resection of the mesial temporal structures. Pathological examination of surgically resected specimens has shown alterations in expression of CB1R of neurons within the hippocampi that provide insight into how disruption of the endocannabinoid system could predispose to epileptogenesis. In resected hippocampi there is a downregulation of CB1R expression on the axon terminals of excitatory (glutamatergic) neurons within the inner molecular layer of the dentate gyrus and an upregulation of CB1R expression on inhibitory (GABAergic) axon terminals within the dentate molecular layer [18]. These changes in CB1R expression result in both a loss of the normal inhibition of excessive glutamate release and increased suppression of GABAergic activity both of which result in increased neuronal hyperexcitability and subsequent seizure generation [22]. In patients with chronic epilepsy, there is also a decrease in the amount of anandamide and 2-AG released with excessive neuronal activation further contributing to a loss of the endocannabinoid mediated inhibition of excessive neuronal activation [18].

The growing body of evidence demonstrating the role the endocannabinoid system plays in the brains' mechanisms in regulating neuronal network oscillations and preventing excessive neuronal hyperexcitability coupled with alterations in the endocannabinoid receptors seen in epileptogenic tissue make the endocannabinoid system an attractive therapeutic target in the treatment of epilepsy. Modulation of the endocannabinoid system would provide a potential novel anticonvulsant mechanism not provided by other anticonvulsant therapies.

4. Phytocannabinoids and epilepsy: mechanisms of action and preclinical studies

The phytocannabinoids are a class of cannabinoids that are produced by plants of the cannabis species. The phytocannabinoids are C_{21} aromatic compounds consisting of an aromatic isoprenyl terpenophenolic core and resorcinyl side chain. Based on the structure of the oxygen bond between the isoprenyl and resorcinyl moieties the phytocannabinoids can be placed into 6 main families. Within each family, variations of the R-chain on the resorcinyl moiety differentiate each individual cannabinoid [23]. To date, over 140 different phytocannabinoids have been identified in *C. sativa.* While there is a high degree of structural preservation among the

phytocannabinoids, they appear to display widely different effects on the mammalian central nervous system. The structural and stereochemical requirements for biological activity of the cannabinoids have been well established. Most biologically active cannabinoids (with a few exceptions) have a hydroxyl group on the C_1 and an alkyl group on the C_3 aromatic positions. As well, naturally occurring cannabinoids are biologically active in the trans (−) enantiomer [24]. Following the first isolation of the cannabinoids it did not take long for their anticonvulsant properties to be recognized [25]. Of the cannabinoids produced by the *C. sativa* the most comprehensively studied in the field of epilepsy are Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD).

Initial research focused on the anticonvulsant effects of Δ^9-THC and other CB1R agonists such as anandamide. Through their activation of CB1R, anandamide and the synthetic cannabinoid WIN 55,212-2 were able to block the production of postsynaptic neuronal spiking and excitatory post synaptic potential production. Both compounds were also able to suppress the production of abnormal burst activity in neurons placed in Mg_2^+ depleted solution. Depletion of Mg^{2+} in solution allows activation of NMDA receptors at normal resting potentials without the usual prerequisite neuronal depolarization. This effect was abolished when CB1R antagonists were added, suggesting that the effect was secondary to activation of CB1R by these agents [26]. Δ^9-THC is a major phytocannabinoid in *C. sativa*. It is a high affinity partial agonist of both CB1R and CB2R that is competitive with both anandamide and 2-AG. The direct activation of CB1R by Δ^9-THC is responsible for its psychoactive effects [19]. Numerous studies have assessed the anticonvulsant activity of Δ^9-THC and its metabolites with conflicting results. These studies showed that Δ^9-THC and its metabolites showed both anticonvulsant and proconvulsant activity depending on the dosage, animal species and seizure model used. In Maximal Electroshock (MES) and Maximal Electroshock Threshold (MEST) mouse models which mimic generalized onset convulsive seizures both Δ9-THC and its metabolites showed anticonvulsant activity by blocking or increasing the latency to hind limb extensor seizures [27]. In other studies Δ^9-THC was also shown to potentiate the effects of several anticonvulsants [28]. In models that showed an anticonvulsant effect of Δ^9-THC, all three of its metabolites including 11-OH-Δ^9-THC showed anticonvulsant effect. The anticonvulsant effect of 11-OH-Δ^9-THC was more potent than its parent compound by almost 1 order of magnitude suggesting that much of the anticonvulsant activity attributed to Δ^9-THC may in fact come from its metabolites [27].

In a rat model of electrically induced limbic seizures Δ^9-THC increased the threshold of electrically induced after discharges at the site of electrode implantation in the left subiculum. However, Δ^9-THC increased the duration of cortically recorded after discharges in electrodes remote from the site of stimulation. This suggested that Δ^9-THC may have both anticonvulsant and proconvulsant effects in focal onset epilepsies [27]. In the cobalt model of focal epilepsy in rats Δ^9-THC increased the frequency of epileptic potentials at the site of the cobalt-induced lesion. This was not seen with Δ^9-THC's main metabolite 11-OH-Δ^9-THC. Both Δ^9-THC and 11-OH-Δ^9-THC seemed to increase generalized cortical excitation as seen by the production of brief intermittent cortically recorded after discharges [27]. Similar findings were seen in a rat model using iron to induce a seizure focus. While both Δ^9-THC and 11-OH-Δ^9-THC both caused increased cortical excitability, only Δ^9-THC provoked clinical seizures. As well, the

dose of Δ^9-THC required to induce seizures was much higher than that required to induce electrographic changes in keeping with cortical excitation [29]. In mice, Δ^9-THC has also been shown to induce kindling of a second epileptic focus in response to both electroconvulsive therapy as well as pentylenetetrazol (PTZ) and picrotoxin induced seizures [30]. When administered to rabbits with a genetic mutation causing audiogenic seizures Δ^9-THC caused signs of neurotoxicity but prevented seizures when the rabbits were stimulated with a sound stimulus above their normal seizure threshold range. Conversely, in another breed of rabbits, injection with Δ^9-THC induced both neurotoxicity and behavioral seizures in a dosage dependent manner [31].

The results of these studies show that Δ^9-THC and its metabolites display anticonvulsant activity in animal models using seizure models with rapidly evoked tonic discharges which mimics certain types of generalized onset seizures in humans. However, in models mimicking focal onset seizures, Δ^9-THC and its metabolites seem to display a proconvulsant effect. This is manifested by increasing the activity at the site of the focal lesion and increasing generalized cortical activity [27]. A proconvulsant effect is also seen in models mimicking genetic based generalized epilepsies and absence seizures. Δ^9-THC and its metabolites seem to induce hypersynchrony with slowly propagating epileptic discharges [32]. While Δ^9-THC showed some potential as an anticonvulsant agent the potential to increase seizure activity along with its neurotoxic and psychotropic side effect profile limited its potential benefit in patients with epilepsy.

CBD is a low affinity negative allosteric modulator of CB1R with no psychotropic side effects due to the fact it does not cause activation of CB1R. It modulates the influx of both Ca^{2+} and Na^{+} into neurons by binding to human T-type voltage gated Ca^{2+} channels, Melastatin and Vanilloid type Transient Receptor Potential membrane receptors (TRPM and TRPV) and voltage gated Na^{+} channels [19]. This decreases neuronal excitability in response to stimulation. CBD has also been shown to inhibit intrasynaptic re-uptake of adenosine as well as activation of neuronal Serotonin, Glycine and Vanilloid receptors [33, 34]. The anticonvulsant effect of CBD is felt to be independent of activation of the endogenous CBR pathways. While the exact mechanism of anticonvulsant activity of CBD remains uncertain it appears to have a polypharmacological effect on modulating neuronal excitability.

In the Cobalt induced focal epilepsy rat model CBD had no effect on focal discharges at the lesion site but decreased the frequency of seizures. CBD also blocked the proconvulsant effects in of Δ^9-THC [27, 35]. In the limbic seizure rat model CBD decreased the frequency, duration and amplitude of electrically induced after discharges at the site of stimulation in the left subiculum but did not prevent the spread of after discharges from the site of focal stimulation to distal electrodes. It had no apparent effect on generalized cortical excitability. This suggests that in focal models of epilepsy, CBD acts directly on the site of focal seizure onset [27].

Other animal studies continued to show the anticonvulsant effect of CBD in both transcorneal electroshock, drug induced and lesional epilepsies. This anticonvulsant effect was seen when a single intraperitoneal (i.p.) dose of CBD was administered alone but like Δ^9-THC it also potentiated the effects of several anticonvulsant medications [33, 36, 37]. While CBD had

potent anticonvulsant effect against tonic seizures its effect against clonic seizures was minimal. Consroe et al. hypothesized that this effect was due to the fact that tonic seizures are spread rapidly throughout the brain from a focal lesion via post-tetanic stimulation. Unlike Δ^9-THC, CBD suppressed tetanic potentiation in isolated bullfrog ganglia [27]. This coupled with the fact that CBD is effective in preventing 3-Mercaptoproprionic acid (3-MPA) induced seizures suggested that some of the anticonvulsant effect of CBD may result from its ability to increase production of GABA in presynaptic GABAergic neurons [36]. Unlike Δ^9-THC, the brain concentrations of CBD correlated well with its anticonvulsant effect in several animal models. This suggests that the anticonvulsant effect of CBD is due to the parent compound and not its metabolites [27].

In summary, CBD was shown to display broad spectrum anticonvulsant activity in a wide range of animal models of epilepsy including generalized seizures caused by electroshock and GABA inhibiting drugs and focal seizures induced by placement of toxic metals on the cortex. It however had no effect on models of generalized absence seizures [38]. CBD also blocked kindling of a second epileptic focus [36]. Even at high doses it failed to cause any behavioral or cognitive side effects in test animals. This would suggest that CBD is a potent anticonvulsant with limited cognitive side effects, making it an attractive potential anticonvulsant in the pediatric population [33, 37].

4.1. Other cannabinoids and terpenes

In addition, Δ^9-THC and CBD several other cannabinoids have been evaluated for the potential anticonvulsant activity. These include Δ^9-tetrahydrocannibivarin (Δ^9-THCV) and cannabidivarin (CBDV) which have been shown to have anticonvulsant effects. Δ^9-THCV is a non-psychoactive cannabinoid that acts as a CB1R antagonist. In a Mg^{2+} depleted solution Δ^9-THCV decreased the amplitude and duration of abnormal neuronal burst activity. Δ^9-THCV potentiated the effects on neuronal bursting of both phenobarbital and valproic acid. In a PTZ rat model Δ^9-THCV did not decrease the severity or duration of seizures or seizure mortality. However significantly fewer rats exposed to PTZ that were treated with Δ^9-THCV displayed seizures compared to those that were given PTZ alone [39]. Like CBD, CBDV is believed to exert its effects via CB1R independent mechanisms and has limited neurotoxicity [40]. CBDV has been shown to decrease the amplitude and duration of abnormal bursting in mouse and rat hippocampal slices in in both Mg^{2+} depleted solution and solution to which 4-aminopyridine (4-AP) has been added. CBDV also significantly decreased the number of seizures seen in in vitro MES and audiogenic seizure models in mice and PTZ induced seizures in rats. Unlike CBD, CBDV also prolonged the latency of seizure induction in a dose dependent manner. Administration of CBDV had no effect on motor performance in mice regardless of the ode administered [41]. The terpenes, which are another class of compounds found in cannabis, also possess a wide range of pharmacological activity on the mammalian nervous system at very low concentrations. Individually, these terpenes have not been assessed in patients with epilepsy [42, 43].

The combinatorial effect of the chemical components of cannabis has been postulated wherein cannabis whole plant extracts may benefit from 'entourage' effects to yield greater effectiveness

than treatment with a purified cannabinoid [42, 44]. This is supported by preclinical studies. In the *in vitro* oxotremorine-M mouse model of epilepsy, excessive neuronal bursting activity can be suppressed with Δ^9-THC, but not CBD, while a standardized cannabis extract containing both Δ^9-THC and CBD can abolish the abnormal bursting activity faster than purified Δ^9-THC alone [45]. In another study, both purified Δ^9-THC and CBD can increase intracellular Ca^{2+} in rat hippocampal neuronal and glial cells. This effect is compounded when the two compounds are mixed together, with the greatest effect occurring with whole plant extract containing both Δ^9-THC and CBD [46]. These preclinical data support the hypothesis that the 'entourage' effects between the various cannabinoids provide therapeutic benefit of cannabis whole plant extract, benefit that exceeds the activity of a single purified cannabinoid. This remains to be demonstrated in the human clinical context.

5. Early clinical experience with cannabis for the treatment of epilepsy

The use of cannabis as a treatment for a variety of ailments in eastern and Mediterranean cultures over the last several millennium has been well documented [47]. The first description of the use of cannabis to treat seizures came from Dr. W. O'Shaugnessy who while working in India reported its successful use to treat seizures in an infant [48]. Following this, cannabis extracts became widely used throughout Europe and North America as an accepted treatment for epilepsy [49]. Following prohibition and with the introduction of other anticonvulsants, cannabis fell out of use as a treatment for epilepsy in western cultures.

During the mid-twentieth century, several reports on the effect of recreational cannabis consumption surfaced with contrasting effects. Several case reports described patients having decreased seizure frequency following the consumption of cannabis [50]. Cannabis consumption was also shown to be protective against first unprovoked seizures. In adult males who smoked cannabis in the last 90 days, the odds of having a first unprovoked seizure was 0.38 compared to adult males who never consumed cannabis [51]. Conversely, a patient with a history of epilepsy who had been seizure free for several months on medication was reported to have had an exacerbation of seizures following the consumption of cannabis [52].

In 1978, Mechoulam et al. reported their double blinded placebo-controlled study of CBD used as an add-on therapy in patients with refractory focal onset seizures. Of the four patients who took CBD two were seizure free for the 3 months of the study while another had partial improvement. None of the five patients who took placebo had any improvement in their seizures [53]. Cunha et al. reported the results of their study investigating the potential of CBD in patients with refractory temporal lobe epilepsy. In the first phase of the study, healthy adult volunteers were randomized to receive either placebo or CBD at 3 mg/kg/day for 30 days. Of 8 volunteers receiving CBD, 2 reported somnolence otherwise no adverse effects were reported. In the second phase, 15 adult patients with drug-resistant temporal lobe epilepsy were randomized to receive either placebo or CBD (up to 300 mg/day) for a period of 18 weeks in a double-blinded manner. Four of 8 patients dosed with CBD had complete improvement while three had partial improvement. No adverse effects were noted in patients given CBD [54].

Two further studies showed no significant difference in seizure reduction with the addition of CBD as an adjunctive therapy. However, in one study patients were given CBD at a dose of 300 mg/day and their plasma CBD levels were maintained at 20–30 ng/ml. Subsequently one participant who had no difference in their seizure frequency was placed on CBD at a higher dose of up to 1200 mg/day. CBD plasma levels were higher averaging 150 ng/ml. This patient had a significant decrease in their seizure frequency suggesting that higher doses of CBD (and higher plasma levels) were required for seizure control [55].

6. Recent clinical trials and experience

In recent years there has been a public perception that cannabis is a potent, natural, and safe alternative therapy for epilepsy. This has driven the demand for and use of cannabis and its derived products to treat epilepsy especially in those patients whose seizures are medically intractable. Coupled with the media exposure showing examples of the apparent miraculous effects of CBD oil in select epileptic patients, treating physicians have struggled to balance the patient demand for cannabis products and the need for studies to determine their, efficacy, dosing, side-effect profile, and indication. To that end, there have been multiple studies, predominantly in children, looking into these clinical questions. Unfortunately, the overwhelming majority of these studies have been retrospective, unblinded, and uncontrolled resulting in their being hampered by various forms of bias and potential placebo effect. Despite the plethora of published research on this topic, questions still remain on the use of cannabis in epilepsy.

In this section, we will review the limitations of the studies, the studies using artisanal and CBD enriched cannabis herbal extracts (CHE), the studies using highly purified pharmaceutical grade CBD, and a meta-analysis of the CBD studies.

6.1. Limitations of the studies

The widespread use of cannabis and the effect of bias are highlighted in various published surveys. McLachlan performed a survey in London, Ontario, Canada, in which more than 60% of patients declared that cannabis was effective for their seizures and stress levels [56]. Ladina et al. reported a case series of 18 patients who all found medicinal cannabis very helpful for seizure control and improvement of mood disorder [57]. By contrast, Press had reported a significant discrepancy in reported responder rate between preexisting Colorado residents and those who moved to Colorado to obtain cannabis to treat their child's epilepsy (22 vs. 47%) suggesting there is a significant perception bias among these children's caregivers as to the therapeutic benefits of cannabis [58]. Physician bias may also play a role as a recent survey by Mathern showed contrasting opinions about CBD between neurologists and the general public. In his study, a minority of epileptologists and general neurologists said that there were sufficient data safety (34%) and efficacy data (28%) and only 48% would advise using medical cannabis and only in severe cases of epilepsy. Conversely, nearly all patients and the general public responded that there was sufficient safety (96%) and efficacy (95%) data, and 98% would recommend cannabis in cases with severe epilepsy [59].

Given the present approved indications for medical coverage, the high cost of pharmaceutical grade CBD products, and the illegal status of cannabis in some countries and US states, the overwhelming majority of patients will at this time be using CBD oil extracts or artisanal products. In many jurisdictions these products are unregulated and therefore their content and consistency are uncertain and can vary. In Australia, where medical use of cannabis is highly restricted, Suraev reported that in parents treating their children with "illicit" cannabis extracts, the majority of extract samples used by the families contained low concentrations of cannabidiol, while Δ^9-THC was present in nearly every sample [60]. These findings highlighted the profound variation in the illicit cannabis extracts being used. Studies examining the use of artisanal and CBD oil extracts therefore could have had uncertain and inconsistent amounts of cannabinoids. This inconsistency in combination the inherent problems of retrospective studies, make the findings of these studies questionable; moreover, none of published studies included serum CBD levels.

To date, there are few prospective, double blind, placebo-controlled studies which all only examined the use of the highly purified, pharmaceutical grade CBD (Epidiolex). None involved artisanal CBD or the CBD oil extracts.

6.2. The artisanal and CBD oil extracts

While keeping the limitations of the studies examining artisanal and CBD oil extracts in epilepsy in mind, most of these studies did find that CBD oil extracts are effective in reducing seizures and improving quality of life.

Tzadok reported out of 74 children being treated with a 20% CBD and 1% Δ^9-THC CHE, 89% reported reduction in seizure frequency with only 43% of patients having a >50% reduction in seizures. Five patients reported aggravation of seizures leading to withdrawal from the study. Improvement in behavior and alertness, language, communication, motor skills and sleep were noted. Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in five patients. The CBD dosing ranged from 1 to 20 mg/kg/day with 83% taking <10 mg/kg/day [61].

Similarly, Porcari retrospectively studied the efficacy of artisanal CBD preparations in children with epilepsy. The study also included a subgroup comparison to determine if the addition of clobazam was related to any beneficial effects of CBD. Overall, the addition of CBD resulted in 39% of patients having a >50% reduction in seizures, with 10% becoming seizure-free. The difference in effect between CBD alone and CBD with clobazam was not statistically significant. Increased alertness and improved verbal interactions were reported in 14% of patients in the CBD group and 8% of patients in the CBD and clobazam group. The average dose of CBD was 2.9 mg/kg/day in the CBD group and 5.8 mg/kg/day in the CBD and clobazam group [62].

McCoy et al. performed a prospective open label study using a 2:100 Δ^9-THC:CBD CHE in 20 children with Dravet syndrome. The dose of CBD ranged from 7 to 16 mg/kg/day (mean 13.3 mg CBD/kg/day). They reported that during the 20-week intervention period the median monthly reduction in motor seizures was 70.6%. The CHE also resulted in improvements

in quality of life measures and spike index on electroencephalogram (EEG). Adverse events during the titration period included somnolence, anorexia and diarrhea [63].

The Cannabinoid Research Initiative of Saskatchewan is currently conducting a Canadian, multicenter, prospective, open-label, dose-escalation phase 1 trial entitled Cannabidiol in Children with Refractory Epileptic Encephalopathy (CARE-E). The source of the CBD oil is consistent with a single batch of 1:20 Δ^9-THC:CBD CHE used for all study participants. Concentrations of the cannabinoids in the CHE were confirmed through Health Canada Quality Assurance and Good Manufacturing Practices (GMP) certification [64]. Preliminary data showed that all 6 participants had improvements in seizure frequency, Quality of Life in Childhood Epilepsy (QOLCE) and EEG rating scores—with three participants showing continued improvements in these measures after the oil extract was discontinued. In addition, serum CBD levels suggested linear dose independent pharmacokinetics in all but one participant. In most participants, serum Δ^9-THC concentrations remained lower than what would be expected to cause intoxication even at the maximum dose of oil extract. None of the participants displayed any evidence of Δ^9-THC intoxication clinically throughout the study. Preliminary data suggests that an effective and well-tolerated CBD initial target dose of 5–6 mg/kg/day is effective and well tolerated when a 1:20 Δ^9-THC:CBD CHE is used. In addition, the serum concentration of CBD follows dose-independent linear pharmacokinetics for most participants, although non-linear pharmacokinetics might occur but requires confirmation. Continued improvement in seizure frequency and QOLCE following the discontinuation of CHE suggest a possible enduring anticonvulsant effect [65].

6.3. The highly purified, pharmaceutical grade CBD products

With the production of a highly purified, pharmaceutical grade CBD (Epidiolex), studies could now be performed with a CBD source of greater reliability. Although potential bias remained, better clinical studies had been performed.

Devinksy published an open label trial in patients aged 1–30 with severe, intractable, childhood-onset, drugs resistant epilepsy. All patients were receiving their regular anti-epileptic drugs. Patients were given CBD at 2–5 mg/kg/day, titrated over a period of 2 weeks till intolerance or to a maximum dose of 25 mg/kg to 50 mg/kg/day. The main objective of the study was to establish safety and tolerability of CBD and the primary end point was the median percentage in the mean monthly frequency of motor seizures at 12 weeks. This study included mainly patients with Dravet and Lennox-Gastaut syndromes. One hundred and sixty-two patients were enrolled. A significant high rate of adverse events was reported in 128 patients (79%). The most common were somnolence (n = 41 [25%]), decreased appetite (n = 31 [19%]), diarrhea (n = 31 [19%]) and fatigue (n = 21 [13%]). This high rate of side effects (many of which were seen during the titration period) suggests that too rapid a titration rate may predispose toward side effects. The median monthly frequency of motor seizures was 30·0 (IQR 11·0–96·0) at baseline and 15·8 (5·6–57·6) at 12 weeks of treatment. The median reduction in monthly motor seizures was 36·5% (IQR 0–64·7) [66].

From this same cohort, Rosenberg et al. reported that caregivers of 48 patients indicated an 8.2–9.9-point improvement in overall patient QOLCE ($p < 0.001$) following 12 weeks of CBD. Subscores with improvement included energy/fatigue, memory, control/helplessness,

other cognitive functions, social interactions, behavior, and global quality of life (QOL). Interestingly, these differences were not correlated to changes in seizure frequency or adverse events. The results suggest that CBD may have beneficial effects on patient QOL, distinct from its seizure reducing effects [67].

Devinsky et al. later performed a double blind, placebo-controlled trial in patients with Dravet syndrome including 120 children and young adults using Epidiolex with a CBD dosage of 20 mg/kg/day. The median frequency of convulsive seizures per month decreased from 12.4 (baseline) to 5.9 with CBD, as compared with a decrease from 14.9 (baseline) to 14.1 with placebo (adjusted median difference between cannabidiol vs. placebo was −22.8% points [CI], −41.1 to −5.4; p = 0.01). The percentage of patients who had at least a 50% reduction in convulsive seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93–4.30; p = 0.08). This study shows an overall benefit of CBD over placebo but also a large placebo effect in the control group [68].

Another trial that assessed the efficacy of Epidiolex in reducing atonic seizures in patients with Lennox-Gastaut syndrome. In this double blind, placebo-controlled trial, a total of 225 patients were enrolled, 76 patients were assigned to a treatment group (20 mg/kg/day CBD) and 76 to the placebo group. The median percent reduction from baseline in monthly atonic seizure frequency during the treatment period was 41.9% in the treatment group vs. 21.8% in the placebo group. As with the other studies assessing Epidiolex, the most common adverse events among the patients in the treatment groups were somnolence, decreased appetite, and diarrhea [69].

A recent systematic review assessed the safety and efficacy of pharmaceutical grade CBD in pediatric onset drug resistant epilepsy with outcome measures including 50% seizure reduction, complete seizure freedom, improved QOL. A total of 36 studies were identified including 6 randomized controlled trials and 30 observational studies. Overall CBD at a dose of 20 mg/kg/day was more effective than placebo in reducing seizure frequency by 50% (Relative Risk 1.74: 1.24–2.43). For one patient to achieve a 50% reduction in seizures the number of patient needed to treat was 8. In pooled data of 17 of the observational studies CBD at 20 mg/kg/day resulted in 48.5% of patients achieving a 50% reduction in seizures (95% CI: 39.0–58.1%) while pooled data from 14 observational studies showed 8.5% of patients became seizure free (95% CI: 3.8–14.5%). Quality of life improved in 55.8% of patients (95% CI: 40.5–70.6%) while serious adverse events related to treatment with CBD was very low at 2.2% of patients (95% CI: 0.0–7.9%). From this data, the authors concluded that pharmaceutical grade CBD may reduce seizure frequency but other randomized controlled trials examining a more diverse group of epilepsy syndromes and other cannabinoids was needed [70].

To date, the evidence to support the use of cannabis in adults is minimal. STAR 1 is a phase 2A, randomized, double blind, placebo-controlled study that evaluated the safety and efficacy of synthetic transdermal CBD in adult patients with focal epilepsy. In this study 174 patients were randomized to receive either 195 mg CBD, 390 mg CBD or placebo via a transdermal patch. Patients who completed the 12-week study were able to continue into the 24-month open-label extension STAR 2 study (n = 171). In as of yet published data from these trials there was an increase in efficacy of transdermal CBD over 18 months. Median percentage change in seizure rates was −25% at 3 months, −40% at 6 months, −48% at 9 months, −52% at

12 months, −57% at 15 months and −55% at 18 months. The transdermal patch was well tolerated. Serious adverse events were as follows: seizures (n = 2) and increased anxiety (n = 1); one death was reported after the 15 month visit. In addition, no significant elevations in alanine aminotransferase and aspartate aminotransferase levels >3 times upper limit of normal were seen [71].

In comparing cannabis derived treatments to standard therapies, it is worthwhile to note that the STICLO group examining the effects of stiripentol in Dravet patients in a double blind randomized placebo controlled study showed that 15 (71%) patients had >50% seizure reduction (including nine free of clonic or tonic-clonic seizures) compared to only one (5%) on placebo (none were seizure free; stiripentol 95% CI 52.1–90.7 vs. placebo 0–14.6). Stiripentol's responder rate is therefore suggested to be superior to Epidiolex with a far lower placebo responder rate [72]. Similarly, in a double-blind, randomized, placebo-controlled trial of the anti-epileptic drug rufinamide in patients with Lennox-Gastaut syndrome, the median percentage reduction in total seizure frequency was greater in the rufinamide therapy group than in the placebo group (32.7 vs. 11.7%, $p = 0.0015$). There was also a difference ($p < 0.0001$) in tonic-atonic ("drop attack") seizure frequency with rufinamide (42.5% median percentage reduction) vs. placebo (1.4% increase). These findings are comparable with the results with Epidiolex. One also has to keep in mind that the median reduction of atonic seizures in the placebo group was markedly higher with the Epidiolex study suggesting potential bias [73].

Of note, the results from the study by McCoy et al. and the preliminary data from CARE-E study showed a much higher responder rate than those with pharmaceutical grade CBD. This apparent superiority of a CHE containing Δ^9-THC would be in keeping with the proposed entourage effect in which the various cannabinoids can act synergistically with one another [42, 44].

7. Conclusion

The cannabinoids found in cannabis appear to offer a unique pharmacological mode of action in the treatment of epilepsy. This, combined with the apparent low risk of serious side effects, makes cannabis and an attractive potential option for patients with treatment resistant epilepsy.

Currently, there is a large public perception that cannabis products are superior to and safer than conventional anti-epileptic medications especially in treating patients with Dravet syndrome and other pediatric onset epileptic encephalopathies. Based on interpretation of the available data, the authors feel that cannabis based therapies show promise in the treatment of children with treatment resistant epilepsies. While the studies to date assessing cannabis based therapies for the treatment of epilepsy have been encouraging, they should be interpreted with caution. At this time, the long-term adverse effects, the indicated epilepsy and seizure types suitable for treatment with cannabis, the dosing of CBD and other cannabinoids, remain unknown. Also, there is minimal data regarding the pharmacokinetics of the cannabinoids especially in children and when used in patients with multiple concomitant medications. Moreover, the existing studies are limited with the majority of them being retrospective and subject to bias, possible placebo effect, and other limitations.

As such, further studies assessing the safety and efficacy of cannabis based therapies in both adults and children are urgently needed. The authors recommend that these studies start with well-designed dose finding studies that include age stratified pharmacokinetic analysis followed by larger scale clinical trials. When faced with physicians that are reluctant to authorize cannabis based products due to a lack of high quality safety and efficacy data, parents who are desperate to help their children are then forced to turn to unregulated suppliers of cannabis. This puts their children at risk of harm and themselves in legal jeopardy.

Author note

Purpose statement: This chapter explores the role of cannabis-based therapies in the treatment of children and adults with epilepsy.

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