Cannabis for Pediatric Epilepsy

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Summary: Epilepsy is a chronic disease characterized by recurrent unprovoked seizures. Up to 30% of children with epilepsy will be refractory to standard anticonvulsant therapy, and those with epileptic encephalopathy can be particularly challenging to treat. The endocannabinoid system can modulate the physiologic processes underlying epileptogenesis. The anticonvulsant properties of several cannabinoids, namely Δ^9-tetrahydrocannabinol and cannabidiol (CBD), have been demonstrated in both *in vitro* and *in vivo* studies. Cannabis-based therapies have been used for millennia to treat a variety of diseases including epilepsy. Several studies have shown that CBD, both in isolation as a pharmaceutical-grade preparation or as part of a CBD-enriched cannabis herbal extract, is beneficial in decreasing seizure frequency in children with treatment-resistant epilepsy. Overall, cannabis herbal extracts appear to provide greater efficacy in decreasing seizure frequency, but the studies assessing cannabis herbal extract are either retrospective or small-scale observational studies. The two large randomized controlled studies assessing the efficacy of pharmaceutical-grade CBD in children with Dravet and Lennox–Gastaut syndromes showed similar efficacy to other anticonvulsants. Lack of data regarding appropriate dosing and pediatric pharmacokinetics continues to make authorization of cannabis-based therapies to children with treatment-resistant epilepsy challenging.

Key Words: Epilepsy, Pediatric, Cannabis, Tetrahydrocannabinol, Cannabidiol.

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EPILEPSY IN CHILDREN AND BASIC PRINCIPLES OF EPILEPTOGENESIS

Epilepsy is a chronic disease characterized by recurrent unprovoked seizures, and diagnosis is made when 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] In Canada, the estimated prevalence of epilepsy in children younger than the age of 14 years is 6.9 of 1,000.[2] The prevalence rates of childhood epilepsy are almost twice as high in the developing world because, in large part, of less access to adequate prenatal care and higher rates of infections and trauma affecting the central nervous system.[3]

Developmental and epileptic encephalopathies are a group of treatment-resistant epilepsy syndromes with onset in childhood that are associated with frequent seizures and poor cognitive, behavioral, and social outcomes as well as developmental stagnation or regression.[4,5] Epileptic encephalopathies include infantile spasms, Lennox–Gastaut syndrome, Doose syndrome, malignant partial seizures of childhood, and the syndrome of continuous spike wave in sleep. Often included in the epileptic encephalopathies is Dravet syndrome, a form of treatment-resistant epilepsy secondary to a mutation within the neuronal-specific SCN1A Na^+ channel. Onset is in early childhood, often with episodes of focal febrile status epilepticus, followed later on by multiple seizure types including generalized tonic–clonic convulsions that may or may not be precipitated by fever. Developmental stagnation or regression often occurs by 4 years of age.[6]

Approximately 70% of children will become seizure-free with their first anticonvulsant medication.[7] The remaining 30% of children with epilepsy will meet the International League Against Epilepsy definition of having drug-resistant epilepsy, which is having failed two or more appropriate anticonvulsant treatments at an appropriate dosage.[8,9] Treatment options for these children are limited to further trials of anticonvulsants, dietary therapies, epilepsy surgery, and neural pathway stimulation.[10] For many children with epileptic encephalopathy who have failed multiple anticonvulsants, the only viable treatment options are the ketogenic diet or neuromodulation. Although these treatments can be of great benefit to children with treatment-resistant epileptic encephalopathy, many children still fail these treatments.[11,12]

Children diagnosed with epilepsy have significantly higher rates of associated mental health and developmental comorbidities including depression, anxiety, learning disability, developmental delay, and autism.[13] A diagnosis of epilepsy in a child is also associated with an increased risk of problems in the domains of independence, social functioning, and school performance.[14] Epilepsy presents a significant financial burden to the health care system, and patients whose epilepsy is resistant to medical treatment place a much higher financial burden of care.[15]

A number of factors that alter the structural and functional integrity of the brain, particularly the cortex, can cause epilepsy in children. This includes ischemic or traumatic injury and genetic, inflammatory, or metabolic abnormalities affecting cortical structure alterations in the structural integrity of the brain. The primary components of epileptogenesis include (1) neuronal hyperexcitability and the generation of abnormal intrinsic burst discharges, (2) a loss of interneuronal inhibition mediated by γ-aminobutyric acid (GABA), and (3) neuronal

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hypersynchrony, allowing these abnormal bursts to spread synchronously within a group of neurons.[16]

There are several unique features of the immature developing brain that make children, particularly newborns and infants, especially prone to seizures.[17] Reduced seizure threshold in young children can be attributed to a tendency toward increased neuronal excitation over inhibition. There are many factors within the immature brain that contribute toward this. Increased cerebral concentrations of glutamate and altered N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor subunit expression result in neurons being more prone to glutamate-mediated depolarization. Decreased cerebral concentrations of GABA and the potential for GABA receptor activation to cause neuronal depolarization further contribute to an enhanced tendency toward excitation.

Owning to altered neuronal Ca^{2+} homeostasis in the immature brain, the influx of Ca^{2+} can also result in endocytosis of GABA receptors and enhanced phosphorylation of KV2.1 channels on the postsynaptic membrane, further impeding neuronal hyperpolarization.[18]

THE ENDOCANNABINOID SYSTEM AND EPILEPSY

Despite being ubiquitously expressed throughout the mammalian brain and playing a major role in neural pathway regulation, the endocannabinoid system and its components were only recently identified. The endocannabinoid system is made up of the two endogenous endocannabinoid receptors (CB1R and CB2R), the endocannabinoid ligands (*N*-arachidonyl-ethanoamide [anandamide] and 2-arachidonoylglycerol), and the enzymes involved in their production and breakdown.[19] Anandamide acts as a partial CB1R agonist, whereas 2-arachidonoylglycerol is a full CB1R agonist. CB1R, which acts as a G-protein–coupled receptor, is expressed on the presynaptic axon terminal. When the postsynaptic neuron membrane is depolarized, anandamide and 2-arachidonoylglycerol are produced from the postysnaptic membrane components and then released into the synaptic cleft, causing presynaptic CB1R receptor activation. This then results in a transient hyperpolarization of the presynaptic membrane through suppression in voltage-gated Ca^{2+} channels and activation of K^+ channels. This transient hyperpolarization of the presynaptic neuron in turn suppresses further neurotransmitter release.[20]

During an epileptic seizure, excess glutamate release from presynaptic excitatory neurons results in presynaptic CB1R activation. The negative feedback mechanism supplied by the CB1Rs decreases the release of further excessive glutamate and prevents further neuronal hyperexcitability, which may play a role in terminating seizures. The increased production of anandamide may prevent seizure-induced excitatory neurotoxic effects.[21,22]

Examination of surgically resected epileptogenic brain tissue in human epileptic patients has shown downregulation of CB1R on the axon terminals of glutaminergic neurons, causing a loss of normal inhibition of glutamate release. In addition, there is an upregulation of CB1R expression on GABAergic axon terminals that would further suppress GABA release.[21] Both of these changes result in a tendency toward neuronal hyperexcitability leading to seizure generation.[23] The role that the endocannabinoid system plays in epileptogenesis provides a pharmacological basis to investigate the use of exogenously produced cannabinoids such as the phytocannabinoids produced by the cannabis plant to treat epilepsy.

PHYTOCANNABINOIDS AND EPILEPSY: A REVIEW OF MECHANISMS OF ACTION AND PRECLINICAL STUDIES

More than 140 unique compounds called phytocannabinoids have been identified in cannabis. Individually and collectively, these compounds appear to have a wide variety of effects on the mammalian central nervous system.[24] To date, the most extensively studied phytocannabinoids for their anticonvulsant properties are Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD). The anticonvulsant effect in these studies varied greatly between species, making extrapolation of dosage and efficacy from animal to human studies challenging. Cannabinol and CBD were first isolated in 1940 and THC in 1942.[25,26] The structure of CBD was characterized by Mechoulam and Shvo in 1963, followed by their elucidation of the structure of THC in 1964.[27,28]

Δ^9-tetrahydrocannabinol is a high-affinity partial CB1R agonist, and it was the first phytocannabinoid to be assessed for its anticonvulsant activity. The anticonvulsant effect of Δ^9-THC is thought to be secondary to its effect on CB1R.[29] There have been numerous *in vitro* and *in vivo* studies performed to assess the anticonvulsant activity of Δ^9-THC and its metabolites, with results varying between the seizure models and animal species used. Both Δ9-THC and its metabolites displayed an anticonvulsant effect in mouse models of generalized epilepsy and potentiated the effects of several anticonvulsants including phenobarbital and valproic acid.[30,31] The anticonvulsant effect of Δ^9-THC's main metabolite, 11-OH-Δ^9-THC, was significantly more potent than that of Δ^9-THC.[30]

In rat models mimicking focal-onset seizures, Δ^9-THC and its metabolites showed both proconvulsant and anticonvulsant activity.[30,32,33] Although Δ^9-THC demonstrated some anticonvulsant potential, the likelihood that it could exacerbate seizure activity and its psychotropic effects limit therapeutic application in children with epilepsy.

Cannabidiol is a partial negative allosteric modulator of CB1R whose anticonvulsant effect is independent of activation of the endocannabinoid system. Neuronal depolarization appears to be reduced by CBD's modulation of Ca^{2+} and Na^+ ion influx into the neuron by binding to human T-type voltage-gated Ca^{2+} channels and by melastatin- and vanilloid-type transient receptor potential membrane receptors and inhibition of intrasynaptic reuptake of adenosine and activation of neuronal serotonin and glycine receptors.[34–36]

The anticonvulsant effect of CBD has been confirmed in multiple animal models of generalized and focal-onset epilepsy both in isolation and when combined with several anticonvulsants whose effects it potentiated.[30,37–39] Cannabidiol's anticonvulsant effect correlated well with its concentration in the brain,

suggesting that the anticonvulsant effect is not a result of metabolites of CBD but rather of the parent compound.[34]

In summary, CBD appears to act as a broad-spectrum anticonvulsant in both generalized and focal-onset seizures.[40] Even at high doses, there did not appear to be any associated behavioral or cognitive side effects. These characteristics make CBD an attractive potential anticonvulsant in the pediatric population.[35,39]

Recently, there has been interest in the potential anticonvulsant effects of the other cannabinoids found in cannabis. Both Δ^9-tetrahydrocannibivarin and cannabidivarin have demonstrated anticonvulsant effects in rodent models of epilepsy, and both have limited potential neurotoxicity.[39,41–43] Δ^9-tetrahydrocannabivarin acts as a nonpsychoactive CB1R antagonist, whereas cannabidivarin is believed to exert its anticonvulsant effects through CB1R-independent mechanisms.[39,41] In addition to having its own anticonvulsant activity, Δ^9-tetrahydrocannabivarin also potentiated the effect of several anticonvulsants.[41]

Terpenes are another class of compounds found in cannabis that are responsible for its characteristic odor. There are more than 200 terpenes found in cannabis, and only a few have undergone any pharmacological evaluation. Some appear to possess pharmacological activity on the mammalian nervous system at very low concentrations, but they have not been assessed in patients with epilepsy.[44,45]

It has been postulated that whole-plant extracts of the cannabis plant may be more effective than individual cannabinoids because of the combined pharmacological effects of all of the cannabinoids present in the plant. Although this "entourage" effect has been suggested in some preclinical studies, such effects remain to be proven in humans.[44,46–48]

HISTORICAL REVIEW OF THE USE OF CANNABIS TO TREAT PEDIATRIC EPILEPSY

Cannabis has been used for a variety of purposes for at least 12,000 years. The earliest artifacts have been found in China, where evidence of the use of cannabis fibers extends as far as 10,000 to 12,000 years in the historical record. Cannabis was also cultivated extensively for its seeds, which were used as a food source.[49] According to oral tradition, Emperor Shen-Nung (ca. 2700 BC) used flowers from the female cannabis plant to treat dysmenorrhea, constipation, symptoms of malaria, gout, and rheumatic disease, although there were few written references to any medical uses of cannabis in ancient Chinese texts until about the second century AD when the Pen-ts'ao Ching was composed.[50]

The earliest known explicit reference to the use of cannabis to treat epilepsy was in Babylonia between 718 and 612 BC. Translations of cuneiform tablets in the collection of the British Museum indicate that cannabis was used effectively to treat a number of different seizure types including nocturnal seizures.[51] Few other references are found in the medical literature until a treatise on hashish written in 1464 and attributed to Abu Bakr Muhammad ibn Zakariya al-Razi, a Persian physician who was chief physician of hospitals in Baghdad and Raghes. al-Razi describes how the poet Ali ben Makki used hashish to successfully treat the seizures of the son of the chamberlain of the Caliphate Counsel.[52]

It was not until Dr. William Brook O'Shaughnessy's 1840 treatise "On the Preparations of the Indian Hemp, or Gunjah," in which he describes his observations in India of the use of cannabis while serving as a physician with the British East India Company, that the use of cannabis as a medicine entered mainstream medical practice. Dr. O'Shaughnessy[53] described his successful use of a cannabis extract to treat infantile spasms in a 40-day-old infant in Calcutta. On his return to Britain in 1842, Dr. O'Shaughnessy lectured widely on his discoveries in India and introduced *Cannabis indica* to his medical colleagues who enthusiastically embraced it.

It was not long before American physicians followed suite, and *Cannabis indica* was included in the U.S. Dispensatory, the forerunner of the Pharmacopoeia, beginning in 1851. The Dispensatory stated that "The complaints in which it has been specially recommended are neuralgia, gout, rheumatism, tetanus, hydrophobia, epidemic cholera, convulsions, chorea, hysteria, mental depression, delirium tremens, insanity, and uterine hemorrhage."[54]

Reports of the effective use of cannabis extracts to treat epilepsy and a number of other conditions became more common in the United States over the next several years, and a committee of the Ohio State Medical Society was convened in 1860 to gather those reports and to comment on the purported benefits of *Cannabis indica*. The chairman of the committee, Dr. R.R. McMeens, reported that he had used an alcohol extract of *Cannabis indica* to successfully treat a case of infantile convulsions and reported on the experiences of a number of other physicians who had used cannabis extracts to successfully treat a variety of different symptoms and illnesses.[55]

Cannabis extract remained a mainstay of medical treatment of a variety of different conditions including epilepsy throughout the 19th and early 20th centuries and was included in the Pharmacopeia of the United States until 1942, despite it having been effectively banned with the passage of the Marihuana Tax Act in 1937. Despite the ban, anecdotal reports of the efficacy of cannabis in the treatment of epilepsy persisted.[56–58]

Mechoulam and Carlini were the first to conduct a placebo-controlled study of CBD in addition to conventional therapy in patients with refractory epilepsy. Two of four patients randomized to the CBD intervention group had complete resolution of their seizures, whereas none of the five patients in the placebo group evidenced any reduction in seizure activity.[59] Subsequently, several groups in Brazil studied the specific use of CBD to treat seizures. In 1980, in a small double-blinded, placebo-controlled trial, Cunha and his group administered 3 mg/kg of CBD to eight patients with poorly controlled epilepsy. Four of eight subjects became seizure-free, while another three subjects experienced improvement in their seizures.[60] One year later, Carlini and Cunha.[61] found that seven of eight subjects with treatment-refractory epilepsy benefited from 200 to 300 mg of CBD per day.

Other small-scale studies of CBD as an antiepileptic were conducted with variable results until the anecdotal report of the successful treatment by Shackelford of refractory generalized tonic–clonic seizures in a child with Dravet syndrome with a

CBD-rich cannabis extract was broadcast in August 2013 by Dr. Sanjay Gupta, the medical correspondent for Cable News Network.[62] This resulted in a dramatic and sustained increase in interest in cannabis and CBD, particularly as a potential treatment for epilepsy. Large numbers of children moved to Colorado in hopes that CBD-rich cannabis extracts might prove effective in their cases as well.

RECENT STUDIES ASSESSING THE EFFICACY OF CANNABIS AS A TREATMENT FOR PEDIATRIC EPILEPSY

Dr. Gupta's report on Cable News Network resulted in a resurgence of interest in cannabis for children with treatment-resistant epilepsy. As a result, there have been several recent studies assessing the efficacy of cannabis in this patient population, but the majority were retrospective, unblinded, or uncontrolled, resulting in significant potential for reporting bias and placebo effect. There are only a few prospective, double-blind, placebo-controlled studies, all of which used the highly purified, pharmaceutical-grade CBD, Epidiolex.

The effect of bias in parental reporting of the beneficial effects of cannabis in children with epilepsy was highlighted by the press's report in which responder rates in children who moved to Colorado were much higher than in children who were pre-existing Colorado residents.[63]

Pharmaceutical-Grade CBD Including the Epidiolex Studies

In the past 5 years, there have been several studies assessing the use of pharmaceutical-grade CBD in children with treatment-resistant epilepsy. These include the recently published randomized placebo-controlled clinical trials of Epidiolex (pharmaceutical-grade CBD-GW Pharma) in children with Dravet and Lennox–Gastaut syndromes that garnered much attention. Although these trials showed overall benefit with pharmaceutical-grade CBD, there was a significant placebo effect seen.

The first publication was an open-label trial with Epidiolex in patients with treatment-resistant epilepsy that included both adults and children, many of whom had either Dravet or Lennox–Gastaut syndrome. A total of 162 participants were enrolled and were given Epidiolex in escalating doses up to 50 mg CBD kg/day in addition to their pre-existing anticonvulsant therapies. The authors reported a median reduction in motor seizures of 36.5% (interquartile range 0–64) after 12 weeks of treatment with CBD compared with baseline.[64] During this study, 48 participants were recruited into a substudy to assess changes in Quality of Life in Childhood Epilepsy (QOLCE) scores with CBD treatment. The total QOLCE scores reported by caregivers improved by a range of 8.2 to 9.9 points during the study with improvements in several subscores including memory, cognitive function, energy/fatigue, social interactions, and behavior. These improvements in QOLCE scores did not correlate with improvements in seizure frequency.[65]

Devinsky et al. also reported a double-blind, randomized, placebo-controlled trial assessing the efficacy of Epidiolex in controlling seizures in patients with Dravet syndrome. This study included 120 children and young adults. During this study, the participants were randomized to receive either placebo or pharmaceutical-grade CBD (Epidiolex) at 20 mg CBD/kg per day. In those randomized to receive CBD, the dose was titrated upward over a period of 2 weeks. In participants who received CBD, the median monthly seizure frequency decreased from 12.4 at baseline to 5.9 once on full dose of CBD. Participants in the placebo group had no significant decrease in median monthly seizure frequency during the study, decreasing from 14.9 at baseline to 14.1 at the study's end. The adjusted median difference between CBD versus placebo was −22.8 percentage points (confidence interval, −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 CBD and 27% with placebo (odds ratio, 2.00; 95% confidence interval, 0.93–4.30; $P = 0.08$).[66]

One more trial assessed the efficacy of Epidiolex on atonic seizures in patients with Lenox–Gastaut syndrome. In this double-blind, placebo-controlled trial, a total of 225 patients were enrolled, with 76 patients being assigned to treatment with CBD and 76 to placebo. The median percent reduction in atonic seizures from baseline during the treatment period was 41.9% in participants taking 20 mg CBD/kg per day versus 17.2% in the placebo group.[67] In both clinical trials using Epidiolex, there were high numbers of participants reporting side effects, namely, somnolence, fatigue, diarrhea, vomiting, and decreased appetite.[66,67] This may have been secondary to the short titration phase at the beginning of each of these studies.

Two systematic reviews of clinical trials assessing pharmaceutical-grade CBD in children with epilepsy treatment were published last year. In the first systematic review reviewing data from 17 observational studies showed that CBD at 20 mg/kg per day was more effective than placebo and resulted in 48.5% of patients having a 50% reduction in seizures and QOLCE scores improved in 55.8%. Serious adverse events were infrequent at 2.2%.[68] The second systematic review analyzed the data of the four Epidiolex clinical trials in children with treatment-resistant Lennox–Gastaut and Dravet syndromes. The pooled average difference in seizure frequency between placebo and CBD at 20 mg/kg per day was 19.9% in favor of CBD. A seizure frequency reduction of 50% (for all seizure types) was 37.2% with CBD at 20 mg/kg per day and 21.2% with placebo.[69]

Studies Assessing Whole-Plant and Artisanal Cannabis Extracts

Many patients are not able to access pharmaceutical-grade CBD because of either financial or regulatory constraints and therefore must turn to CBD oil extracts or artisanal products. In many jurisdictions, these artisanal products are poorly regulated and can vary widely in content even when made by the same producers. Suraev et al.[70] reported that the majority of artisanal cannabis extracts used by Australian families to treat their epileptic children contained low concentrations of CBD, while Δ^9-THC was present in nearly every sample. The inconsistency of these cannabis products, combined with the inherent problems of retrospective studies, makes the findings of many of the

studies assessing whole-plant cannabis herbal extracts (CHEs) challenging to interpret. None of the published studies included serum CBD levels.

Most studies examining artisanal and CBD-enriched CHE oil in epilepsy showed efficacy in reducing seizures and improving quality of life in children with epilepsy. Tzadok et al. reported in a study of 74 children with treatment-resistant epilepsy that a 20:1 CBD:Δ^9-THC CHE resulted in 89% of children reporting a reduction in seizure frequency and 43% of patients having a greater than 50% seizure reduction. Five participants reported aggravation of seizures which led to withdrawal from the study. Improvements were noted in alertness, sleep, behavior, and language, communication, and motor skills. Adverse reactions were similar to those seen with pharmaceutical-grade CBD, leading to withdrawal from the study in five patients. Cannabidiol dosing ranged from 1 to 20 mg/kg per day with 83% taking $<$10 mg/kg per day.[71] The retrospective study by Porcari et al. on the efficacy of artisanal CBD preparations in children with epilepsy demonstrated that addition of CBD resulted in 39% of patients having a $>$50% reduction in seizures, with 10% becoming seizure-free.[72] In a subgroup analysis, coadministration of clobazam did not have a significant effect in the efficacy of CBD. Coadministration of clobazam with CBD resulted in slightly lower improvements in alertness and verbal interactions compared with those not taking clobazam concomitantly with CBD (8% vs. 14%). In McCoy et al.'s prospective open-label study using a 2:100 Δ^9-THC:CBD CHE in 20 children with Dravet syndrome, CBD doses ranged from 7 to 16 mg/kg per day (mean 13.3 mg CBD/kg per day). The median monthly motor seizure reduction was 70.6% during the 20-week intervention period. The authors also reported improvements in quality of life measures and spike index on EEG. Adverse events during the titration period were similar to those reported in other studies.[73]

The Cannabinoid Research Initiative of Saskatchewan is currently conducting the Cannabidiol in Children with Refractory Epileptic Encephalopathy trial, which is a multicenter, prospective, open-label, dose-escalation phase 1 study using a Health Canada 1:20 Δ^9-THC:CBD CHE.[74] Preliminary data of seven participants showed all had improvements in seizure frequency, QOLCE, and EEG rating scores. Even at the maximum dose of the CHE serum, Δ^9-THC concentrations remained lower than expected to cause intoxication in most participants, and none of them displayed any evidence of Δ^9-THC intoxication. Preliminary data suggest that an effective and tolerated CBD initial target dose is 5 to 6 mg/kg per day. Although most participants had dose-independent linear pharmacokinetics of CBD, one participant showed nonlinear CBD pharmacokinetics when CBD doses were above 8 to 9 mg/kg per day, suggesting caution is required when using higher CBD doses. Continued improvement in seizure frequency and QOLCE in three participants after the discontinuation of the CHE suggests a possible enduring anticonvulsant effect.[75]

Overview of Clinical Studies in Children

Although there is a pervasive and widespread public perception that cannabis products are safer and more effective than conventional therapies in the treatment of seizures due to Dravet syndrome and other pediatric epileptic encephalopathies, it is important to important to note that Chiron et al. who examined the effects of stiripentol patients with Dravet syndrome with a double-blind, randomized, placebo-controlled study showed that stiripentol's responder rate was superior to that seen in the Epidiolex studies with a far lower placebo responder rate.[76] In a double-blind, randomized, placebo-controlled trial in patients with Lennox–Gastaut syndrome, rufinamide resulted in a decrease in atonic seizures that was similar to those seen in the Epidiolex studies. In the Epidiolex study, the median seizure reduction in the placebo group was higher, suggesting a greater influence from observer bias.[77]

In comparison with the response rate reported in studies using pharmaceutical-grade CBD, a much higher responder rate was reported by McCoy and seen in the preliminary data from the Cannabidiol in Children with Refractory Epileptic Encephalopathy study with a CHE that contained low levels of Δ^9-THC. This apparent superiority of the CHE gives credence to the proposed entourage effect in which the various cannabinoids interact synergistically to produce a greater clinical effect.[44,46] A meta-analysis comparing the efficacy of pharmaceutical-grade CBD with whole-plant CHE of clinical studies to date found a larger percentage of children taking CHE had a reduction in seizure frequency compared with pharmaceutical-grade CBD (71% vs. 46%; $P < 0.0001$) with lower daily CBD doses when a CHE was used.[78]

SIDE EFFECT PROFILES OF CANNABIS-BASED THERAPIES IN CHILDREN WITH EPILEPSY

There remains significant concern among physicians and regulators regarding the potential harmful effects of cannabis-based therapies in children. Of particular concern is the potential for intoxication from Δ^9-THC and its effects on brain development. Although most pediatric epilepsy studies reported high rates of side effects in children taking cannabis (51%), these side effects tended to be mild. Reported side effects included sleepiness, fatigue, and gastrointestinal symptoms such as nausea, diarrhea, and decreased appetite. Rare but potentially serious side effects reported included elevations of liver enzymes (particularly in children taking valproic acid concurrently), worsening of seizures, and blood dyscrasias. Surprisingly, the rate of side effects seems to be higher in patients taking pharmaceutical-grade CBD compared with those taking CHE.[78] This may relate to the rapid dosage titration schedules used in the pharmaceutical-grade CBD studies.[66,67] In the six participants who completed the Cannabidiol in Children with Refractory Epileptic Encephalopathy study, only two had trough plasma steady state. Δ^9-THC concentrations remained low even when taking a 1:20 Δ^9-THC:CBD CHE at a dose of 10 to 12 mg/kg per day. Intoxication from Δ^9-THC is unlikely when using pharmaceutical-grade CBD or low Δ^9-THC extracts because CBD is thought to attenuate the potential intoxicating effects of Δ^9-THC.[79] Although there is no published long-term safety data regarding the use of pharmaceutical-grade CBD or CBD-predominant CHE in children, the potential developmental

effects of the cannabinoids need to be weighed against the potential neurodevelopmental harm caused by uncontrolled seizures.

EFFECT OF CANNABIS ON EEG

To date, only three studies assessing the efficacy of CBD in children with refractory epilepsy included EEG as part of the evaluation. In McCoy et al.'s[73] open-label study of children with Dravet syndrome, 16 participants completed two 24-hour ambulatory EEGs with one baseline study recorded before commencing the CHE and the other at the maximum dose of 1:50 CHE. In these recordings, the spike per second index was reduced from 0.09 to 0.06 ($P = 0.022$) with significant reductions seen in 10 participants. There appeared to be a correlation between reduction in spike per second index on EEG and reduction in seizure frequency. A nonsignificant reduction in electrographic seizures was also noted.

A retrospective review of children with refractory epilepsy taking pharmaceutical-grade CBD also analyzed EEG recordings from 20 participants. The authors report "CBD may or may not improve EEG background activity and frequency of epileptiform discharges." An improvement in the EEG recording did not necessarily correlate with the improvement in clinical seizure frequency.[80] Huntsman et al.[75] reported that six of the seven participants who had completed the Cannabidiol in Children with Refractory Epileptic Encephalopathy study to date, the use of the 1:20 Δ^9-THC:CBD CHE resulted in an improvement in their EEG background activity, and three participants also had improvement in their EEG spike index with two having resolution of the continuous spike wave in sleep activity.

CONCLUSION

Although all of the studies with cannabis-based therapies and epilepsy have been promising, they should be interpreted with caution. At this time, the pharmacokinetics, the long-term adverse effects, the indicated epilepsy and seizure types, the dosing of CBD, and other cannabinoids remain uncertain. For now, CBD is likely effective in treating various forms of epilepsy, but it has not been shown to be superior or safer than conventional medical therapies.

The observations by 19th and early 20th century physicians suggest that whole-plant extracts made from cannabis can be effective in controlling epilepsy. This, combined with the data from recently performed open-label studies, may indicate that more complex combinations of many different cannabinoids found in the cannabis plant may be more successful as antiepileptics than one single cannabinoid such as CBD alone.

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