

The Use of Cannabidiol as an Adjunct Therapy for Refractory Epilepsy Children:

A Literature Review of Cannabidiol Integrated Therapy

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## **Chapter 1: Introduction**

Epilepsy is a common and chronic neurological disorder which frequently requires the use of polypharmacy in attempts to curb the debilitating seizure episodes and mounting side effects. There are approximately 50 million people suffering worldwide with epilepsy, and approximately 35% of those patients have refractory epilepsies (RE's). The term refractory epilepsy specifically means that the commonly used antiepileptic medications fail to bring patients seizures under control. Sometimes RE is called by other names, such as uncontrolled epilepsy or intractable epilepsy and subsequently falls under the umbrella term of RE's. Epilepsy in general refers to a group of neurological disorders characterized by epileptic seizures. These epileptic episodes can vary from brief and nearly undetectable periods to long periods of vigorous shaking, which often results in a variety of physical injuries. In epilepsy, seizures tend to recur and often have no immediate underlying cause. Patients often experience varying degrees of social stigma due to their condition. According to the World Health Organization, nearly 2.4 million new cases of epilepsy are diagnosed annually (Megiddo, et al., 2016).

### **Epilepsy and the pediatric patient**

For pediatric patients, ages less than 1-18 years old, with rare and complex disorders such as: Dravet Syndrome (DS), Lennox-Gastaut Syndrome (LGS), West Syndrome (WS), Doose Syndrome (DS), Ohtahara Syndrome (OS), and other unspecified refractory epilepsy (URE), there is much suffering and distress. These disorders often have an infantile onset of development and/or develop within the first few years of life, including epileptic encephalopathy associated with drug resistant seizures, and also accompany a high mortality rate. These serious childhood epilepsies are characterized by frequent convulsions, delayed neurological

development, and deterioration in the quality of life for the child. Too often these epilepsy patients require the use of polypharmaceuticals, some displaying resistance of up to 12 different anti-epileptic drugs (AED's) (Aguirre-Velazquez, 2017).

Drug resistant epilepsy (DRE) is a serious and potentially life-threatening disorder that affects the daily functioning of those patients afflicted. Patients with DRE are at a higher risk for sudden unexpected death in epilepsy (SUDEP), which is characterized by the frequency of generalized tonic clonic seizures, the use of numerous anti-epileptic drugs (AED's) being used, and susceptibility for nocturnal seizures are the leading risk factors for SUDEP. Annual SUDEP risk for patients with epilepsy is 1/1000; whereas SUDEP risk for patients with drug resistant epilepsy is 1/150 (CDC, 2018).

Patients with REs either do not respond to or they respond incompletely to the current FDA approved AEDs. Children surviving with drug resistant epilepsies are particularly vulnerable, and are in urgent need of more effective medications because those suffering from early-onset and high seizure burden epilepsies suffer the greatest neurodevelopmental problems, including intellectual disabilities and Autism. In some syndromes, such as Dravet Syndrome, recent evidence suggests that more effective early control of epilepsy is associated with better developmental outcomes than in children who were treated 20-30 years ago (National Center for Chronic Disease Prevention and Health Promotion | Division of Population Health, 2016).

### **Medications to treat epilepsy**

FDA drugs being administered today for epilepsy would include both narrow spectrum and broad spectrum AED's. Some examples of narrow spectrums would include:

Carbamazepine, Clobazam and Diazepam (benzodiazepines), Divalproex, Eslicarbazepine Acetate, Ethosuximide, Gabapentin, Lacosamide, Methsuximide, Oxcarbazepine, Perampanel,

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Phenobarbital, Phenytoin, Pregabalin, Rufinamide, Tiagabine Hydrochloride, and Vigabatrin.

Some examples of broad-spectrum drugs used for epilepsy would include: Clonazepam, Clorazepate, Ezogabine, Felbamate, Lamotrigine, Levetiracetam, Lorazepam, Primidone, Topiramate, Valproic Acid, and Zonisamide (Carter & Cherney, 2016). None of the FDA approved medications for RE are “side effect free” but rather have many SE’s including: drowsiness or difficulty sleeping, dizziness, suicidal thoughts or actions, emotional depression, respiratory depression, electrolyte imbalance, dependence and inability to withdraw, multiple organ issues, urinary retention, blood disorders, hyperactivity, weight gain or weight loss, gastric issues, birth defects, memory loss, tremors, agitation, worsening of seizures, hair loss, vision problems, and metabolic acidosis. In addition, AEDs have interferences with most other medications (Glass, 2009).

In such cases where the child does not respond to conventional treatments of AED’s the results of cannabidiol (CBD) use provides parents with the hope that they may soon have another treatment option for their suffering child. CBD, the non-psychoactive compound that is derived and isolated from the cannabis plant, provides a highly beneficial pharmacologic effect. For centuries cannabis has been known, and used, as one of the oldest psychotropic anticonvulsants. For the past few years several studies have surfaced validating CBD and its use as an adjunct therapy for pediatric patients with drug resistant seizure disorders and rare refractory epilepsies (Verrotti, Castagnino, Maccarrone, & Fezza, 2016).

Several states in the United States (US) as well as the federal government have received a tremendous amount of pressure to legalize the use of cannabis and/or its derivatives for medical purposes, including for RE’s. CBD exhibits neuroprotective, antiepileptic, anxiolytic, antipsychotic, and anti-inflammatory properties (Fasinu, Phillips, ElSohly, & Walker, 2016).

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Currently, 27 states have laws broadly legalizing marijuana, including CBD, in various forms: however, several states have passed more narrow laws allowing residents to possess cannabis or its derivatives only if they suffer from certain rare medical illnesses (Governing, 2018).

### **The research question**

This research will be an integrative literature review of global studies regarding the adjunct use of CBD for the vulnerable population of pediatric RE patients. The research question: Does using CBD as an adjunct therapy in pediatric RE patients lower the episodic number of seizures rather than continuing with polypharmacy and related dose adjustments alone?

## **Chapter 2: Literature Review**

A literature review was conducted as a means of evaluating current research establishing the safety and efficacy of incorporating the use of CBD into the medication regimen of pediatric RE patients who have failed to respond favorably with the use of current AED's. This review has taken precautions to avoid literature bias, taking into consideration that pediatric RE patients are a rare and highly vulnerable population to begin with.

### **Metaanalysis**

Fasinu, Phillips, ElSohly, and Walker (2016) conducted a metaanalysis of 54 studies conducted in the US where CBD was used to measure treatment outcomes of drug-resistant seizures and disorders. Eleven of those studies focused on pediatric RE's. Sample sizes range from ~20 to ~350 patients. This large study looks at the development of CBD and the pharmacology, as well as the toxicology, of Cannabidiol and its medical use within the US. It was noted that cannabidiol has great pharmacologic potential without exerting any significant intrinsic activity on the cannabinoid receptors, whose activation results in the psychotropic effect that would be recognized from the use of tetrahydrocannabinol (THC), the main chemical component found in Cannabis. Should these chemicals not be isolated and gleaned out prior to medicinal administration to fragile pediatric patients. CBD has "great potential utility, but uncertainties remain regarding sourcing, long-term safety, abuse potential and regulatory dilemmas" as to Federal Regulations and Schedule 1 classification (Fasinu et al., p. 1). Based on CBD's long history of use and the large numbers of studies now under way, various medical conditions are being assessed for the incorporated use of cannabidiol. One particular study is being conducted in the US as a means of assessing the use of CBD for anxiety. This study has recruited approximately 16 people, all of which are 18 years of age or older, with the primary

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end result of determining any change in anxiety symptoms via the Beck Anxiety Inventory. An additional study under way is being conducted in Israel as a means of assessing CBD's anti-inflammatory effects for patients with bowel diseases; this study includes 20 patients, ages 20-80. Another study is being conducted in the United Kingdom on the use of CBD for diabetes mellitus (DM) patients; this study includes 62 people, all of which are over the age of 18, the study is monitoring the mean serum HDL levels for changes from baseline with the incorporated use of CBD. (Fasinu et al., p. 8). The incorporated use of CBD is an area of practice to continue to monitor for its potential use for RE patients. Other studies now being conducted, both in the US and in the Netherlands, one which assessed a group that included approximately 86 patients of ages 1-30 years old, another which included approximately 120 patients of ages 2-18 years old, and one other study group of approximately 150 patients, ages 50 or younger. The largest group studied is approximately 350 patients, two years of age or older, and another study includes 80 patients aged 2-18 years old. These studies assessed Dravet Syndrome patients as a means of determining if there was any reduction in the numbers of seizures, the number of adverse effects seen, and the adjunct treatment of traditional AED's used while incorporating CBD into the plan of care (Fasinu et al., p. 9).

Stiripentol is an anticonvulsant drug used for the treatment of Dravet syndrome. It is unrelated to other anticonvulsants and belongs to the group of aromatic allylic alcohols. It is used in some countries as an add-on therapy with sodium valproate and clobazam for treating children with Dravet syndrome whose seizures are not adequately controlled. Epidiolex, a purified cannabinoid that comes in a liquid form containing CBD and no THC, currently undergoing clinical trials in the US, is being developed by GW Pharmaceuticals, in Salisbury, UK. It has been granted orphan drug status for the treatment of Dravet and Lennox Gastaut syndromes

(Fasinu et al., p. 6). Within the analysis are other current studies, such as one being conducted in the USA of approximately 120 patients ranging in ages from 2 to 55, as a means of assessing for reductions in the number of seizures when Epidiolex is used as an adjunct therapy along with the common AED's. Another study being conducted in the USA regarding the use of Epidiolex includes approximately 80 patients, also ranging in ages of 2 to 55, to assess the effect of adjunct therapy in regards to the potential reduction in number of seizures (Fasinu et al., p. 11). These current studies are being performed as a means to monitor the drug-drug additive effect of CBD use along with other common AED's given to pediatric patients. Parents, along with physicians, can then make sensible decisions regarding necessary efforts for the gradual withdrawal of common AED's based on the long term side effects noted in other drug SE studies.

### **Study survey**

Cilio, Thiele, and Devinsky (2014) conducted a survey performed in the United States that included 19 parents of RE patients, 12 whom had children with a diagnosis of Dravet Syndrome. During a three-month-trial of CBD as an adjunct to the children's regular medication regimen, 42-53% reported a greater than 80% reduction in seizure frequency, and 11% were seizure free. Also noted was an improved alertness in children and better mood and sleep, with no reported severe side effects other than drowsiness and fatigue. This study supports previous research regarding the efficacy and thus validity of CBD as an adjunct medication versus continued use of poly AED's and/or related dose adjustments alone based on its large percentage of success. Due to the small sample size, placebo effect cannot be entirely eliminated as a contributing factor to the research outcome (Cilio et al., p. 2). This study calls for the US to lift federal laws that prohibit CBD's use, along with its stringent Schedule I drug classification, and outlines the need for the licensure of CBD use, which is already implemented in many other

countries, such as Canada, the Netherlands, and Israel (Wachtel, Ross, ElSohly, Ambre, & de Wit, 2002).

### **Retrospective cohort study**

Tzadok, et al., (2016) conducted a retrospective cohort study via clinical records from both office and telephone call visits. Seventy four patients with RE's resistant to greater than seven AED's met the inclusion criteria. Four Israeli pediatric epilepsy clinics, with patients whose ages ranged from 1-18 years old and diagnosed with RE's, were administered a regimen of medical CBD. This study divided the patients into 6 groups based on their seizure etiology. The CBD yielded a significant positive effect on seizure load. Eighty-nine percent of children reported a reduction in seizure frequency: 18% with a 75-100% reduction, 34% with a 50-75% reduction, and 12% with a 25-50% reduction. Five percent reported an aggravation of seizures. The participants also reported improvement of behavior; including, alertness, language, communication, motor skills, and sleep. Adverse effects reported from CBD use were: somnolence, fatigue, GI upset, and irritability, which led few to the withdrawal of CBD in their medication regimen. The incorporated use of CBD to the RE medication regimen were encouraging as a treatment option for RE. Well-designed clinical trials are further warranted to incorporating CBD's use into the existing RE medication regimen including the decreased use of the traditional AED polypharmaceuticals (Tzadok, et al., p. 3).

### **Structured online survey**

Aguirre-Velazquez (2017), conducted a structured online survey taken from a group of parents whose children were diagnosed with RE and also using CBD. The online survey consisted of commercial software that provided options for an unlimited number of questions of different types (open, closed, and multiple choices). The survey consisted of 31 questions in nine

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sections. The sections included: personal details, time of evolution and neurological diagnosis, previous number of conventional AED's prior to the use of CBD, total number of seizures in the month preceding CBD treatment, CBD product, dose and time of treatment, total number of seizures in the month following CBD treatment, changes in emotional, cognitive, sleep, and dietary state, side-effects observed during treatment with CBD, and open feedback on the use of CBD. The survey was available for the month of September, 2016. The system gathered responses and produced a report using basic statistical analysis. Fifty-three cases were selected which met the research criteria of an RE diagnosis and while using Cannabinoid. The ages of these children were between nine months and eighteen years of age. Forty-three of the cases were from Mexico and ten were from other Latin American countries (Aguirre-Velazquez, p. 2). Forty-seven percent of the patients had been previously treated with nine or more AED's. With CBD used as an adjuvant therapy, 81.3% reported a decrease in seizures, 51% reported a moderate to significant decrease, and 16% were free from seizures. The number of AED's that had been used was then reduced in 20.9% of those cases. No serious side effects were reported. Some mild adverse effects were reported with the addition of CBD, such as, increased appetite or changes in sleep patterns reported in 42% of cases (Aguirre-Velazquez, p. 1). It was concluded that the parents of the studied RE patients would classify CBD as "useful" as an adjunct therapy for RE children. In spite of this relatively small in number sampling size, the protocols used within this study establishes positive results for the adjunct use of CBD. Based on these findings, these protocols can be duplicated in larger centers with an increase number of candidates who would meet the inclusion criteria. Further research to include double blinded cohort studies in other countries would further enhance the validity and reliability of findings (Aguirre-Velazquez, p. 5).

**Investigational new drug trial**

In an investigational new drug (IND) trial by Geffery, Pollack, Bruno, and Thiele (2015), conducted in the USA, 25 patients with RE were selected and studied. Of the 25 study participants, 13 were treated with clobazam (CLB) and CBD simultaneously. Clobazam is used with other medication(s) to control seizures in adults and children two years of age and older who have Lennox-Gastaut syndrome (Geffrey et al., p. 1). Clobazam is in a class of medications called benzodiazepines. It works by decreasing abnormal electrical activity in the brain. Demographic information was gathered for each patient, which included age, gender, and etiology of seizures, as well as the concomitant use of AED's (Geffrey et al., p. 2). Children and caregivers were interviewed either in person, over the phone, or emailed. Of the 13 being treated with CLB and CBD varied adverse side effects (SE) were reported such as ataxia, restless sleep, urinary retention, drowsiness, irritability, tremors, and loss of appetite. Throughout the study CBD dosing was either decreased, due to SE's or kept constant and patients' blood levels were drawn and analyzed over the four to eight week study period. Nine of the thirteen CLB/CBD patients reported having a greater than 50% decrease in seizures, corresponding to a responder rate to the study survey of 70%. The mean change in seizure frequency was decreased by 56%. Only two patients had an increase in seizure frequency (14%). Both of these patients had their CLB dose decreased over the course of the study; the CBD adjunct treatment was then well tolerated. Due to the fact that both CLB and CBD are metabolized in the cytochrome P450 pathway (CYP), a drug-drug interaction was noted with CLB and CBD when metabolized; reduction of the antiepileptic drug CLB dose alleviated consequential SE's and all subjects continued to tolerate CBD well throughout the trial (Geffrey et al., p. 1). CBD appeared safe and effective in pediatric patients on CLB treatment for RE's.

**Nationwide survey**

Suraev, et al., (2017) conducted a nationwide Australian online survey of experiences with CBD for epilepsy treatment. The survey consisted of 39 questions assessing demographics, clinical factors including diagnosis and seizure types, past treatment with AED's, and experiences with and opinions towards cannabis use in epilepsy. A total of 976 responses met the inclusion criteria and the survey was posted for 10 days (Suraev, et al., p. 2). The results showed that a total of 15% of adults with epilepsy and 13% of parents with epileptic children were currently using or had used CBD as adjunct therapy and of those, 90% of adults and 71% of parents reported success in reducing seizure frequency. Almost one half of the respondents with a history of CBD use reported a reduction in the amount of AED's used after the initiation of adjunct CBD therapy. The number of past AED's tried was a significant predictor of CBD use in both adults and children with epilepsies. RE's and dissatisfaction with the side effects of AED's were the two main reasons for trying CBD (Suraev, et al., p. 5). Further studies regarding the knowledge of efficacy, safety, and potential treatment must be considered. The physical side effects of AED's, which included weight gain and tiredness, as well as a decreased quality of life, were better tolerated with CBD as an adjunct medication, but still imposed a considerable burden on patients, however, approximately 50% of all CBD users reported a decrease in some of the AED's used after commencing with the use of CBD products (Suraev et al., p. 6). Responses were uploaded onto an electronic spread sheet and tabulated. Thirty four variables, including demographics and medical history relating to the epilepsy, were tested as potential predictors for medicinal cannabis use. The dependent variable (whether the individual had used medicinal cannabis or not) was dichotomous, and the independent (predictor) variables were a mix of dichotomous and continuous variables. Each independent variable was first entered into a

univariate binary logistic regression analysis. Variables that predicted medicinal cannabis use with a degree of significance of  $p < 0.1$  were entered into a multivariate forward conditional binary regression analysis. Two multivariate analysis were conducted, one for children (less than 18 years) and one for adults ( $\geq 18$  years) with epilepsy. The regression analysis included 65.5% (255/389) children with epilepsy and 57.5% (338/587) adults with epilepsy (Suraev et al., p. 2).

### **Controlled double-blind, placebo controlled trial**

Devinsky, et al. (2017), conducted a double-blind, placebo controlled trial at 23 centers in the US and Europe. 177 patients were screened and of those, 120 met the inclusion criteria of having a diagnosis of Dravet syndrome and/or other drug resistant seizures. The 120 patients were randomly assigned to receive either CBD at a dose of 20 mg/kg/day or a placebo, in addition to standard AED treatment, over a 14-week period. The primary end point was the change in convulsive-seizure frequency during that 14-week period compared with a 4-week baseline period (Devinsky, et al., p. 1). The mean ages of the patients were 9.8 years (range, 2.3 to 18.4) and 52% were male. The baseline convulsive-seizure frequency was a median of 13.0 seizures per month (range, 3.7 to 1717). A total of 108 patients (90%) completed the treatment period (52 of 61 patients [85%] in the cannabidiol group and 56 of 59 patients [95%] in the placebo group). A total of 12 patients (10%) withdrew from the trial prior to completion (9 in the cannabidiol group and 3 in the placebo group). Of the 108 patients who completed the trial, 105 entered the open-label extension study (Devinsky, et al., p. 4). The percentage of patients with at least a 50% reduction of seizure frequency was 43% with CBD and 27% with the placebo. The percentage of patients who became seizure-free was 5% with CBD and 0% with placebo. Among those patient's with Dravets syndrome, CBD resulted in a greater reduction of convulsive-seizure frequency than the placebo group but was also associated with higher rates of adverse events;

16% (CBD) versus 5% (placebo). The noted side effects listed were somnolence (36% with CBD versus 10% with placebo), loss of appetite (28% with CBD versus 5% with placebo), and diarrhea (31% with CBD versus 10% with placebo). These adverse effects could have been related to drug-drug interactions with other commonly used AED's, particularly Valproate. Abnormalities of hepatic aminotransferase levels occurred, which gives rise to the suggestion that CBD may potentiate a Valproic acid-induced change on these hepatic aminotransferase levels. This noted observation, for the most part, resolved while the patients continued taking the AED's that were suggested to have caused a transient metabolic stressor for the liver. The patients overall condition improved by at least one category of the 7-category Caregiver Global Impression of Change Scale in 62% of the CBD group as compared to 34% of the placebo group (Devinsky, et al., p. 1). Analysis of the primary end point was performed with the use of a Wilcoxon rank-sum test. An estimate of the median difference between cannabidiol and placebo, together with the 95% confidence interval, was calculated with the use of the Hodges-Lehmann approach. Sensitivity analysis of this primary end point was prespecified in the trial protocol and statistical analysis plan. The percentage of patients with a reduction in convulsive-seizure frequency from baseline of at least 25%, at least 50%, at least 75%, or 100% was analyzed with the use of a Cochran-Mantel-Haenszel test and presented with odds ratios. The changes from baseline in the Caregiver Global Impression of Change (CGIC) and the Caregiver Global Impression of Change in Seizure Duration (CGICSD) were analyzed with the use of an ordinal logistic-regression model. For the secondary endpoints, there were no adjustments of P values for multiple comparisons (Devinsky, et al., p. 3).

### **Systematic review**

Koppel, et al., (2014) conducted a systematic review of the efficacy and safety of medical marijuana in selected neurologic disorders. The review encompassed 34 studies done in the US, 8 of which were rated as Class I, meaning that the study had a low risk, and that it adheres to commonly held tenets of high quality design, execution and avoidance of bias. Studies were graded according to the American Academy of Neurology (AAN) classification scheme for therapeutic articles (Koppel, et al., p. 1). Of the 1,729 abstracts reviewed, 63 full texts articles were located and 33 were found to meet inclusion criteria of having a neurologic disorder such as Multiple Sclerosis (MS), non-chorea-related symptoms of Huntington disease, epilepsy, Tourette syndrome, urinary dysfunctions, cervical dystonia, levodopa induced dyskinesia in patients with Parkinson disease, tremors, central pain or painful spasms, spasticity related to MS and other neurologic conditions. Also, an updated search in 2013 yielded one more article for inclusion (Koppel, et al., p. 2). From 1948 to 2013, evidence based reviews of seizure frequency and symptom treatment with medical cannabis for epilepsy were examined with the knowledge that the active chemical compound of CBD had been found effective once isolated and extracted in 1963 from the cannabis plant. The concentration of THC present in formulations and the ratio of THC to CBD, which limits the psychoactive effects, played a role in therapeutic effects of cannabis products (Koppel, et al., p. 1). There were no Class II or Class III studies performed; there were 2 Class IV studies that did not demonstrate significant benefit and did not show adverse effects over the 3-18 weeks of treatment. Further research with randomized controlled studies is necessary in order to determine the efficacy of this medication classed as Schedule 1, which may be difficult due to the stigma and additional burden placed on researchers in the USA (Koppel, et al., p. 6).

**Double-blind placebo study**

In an experimental design by Cunha, et al. (1980) a two-phase double-blind-placebo study was conducted in Brazil. Phase one the study consisted of 16 healthy volunteers. Phase 2 consisted of 15 epileptic volunteers. In phase one of the study, 16 adults (11 men and 5 women), and aged 22 to 35 years old, with an average weight of 65 kg were chosen from the staff of Escola Paulista de Medicina. They were in good health, showing neither clinical nor laboratory evidence of cardiovascular, renal, hepatic, or other impairments (Cunha, et al., p. 3). Within phase 1 of the study, 3 mg/kg/day of cannabidiol (CBD) were given for 30 days to 8 healthy volunteers. Another 8 volunteers received the same number of identical capsules containing glucose as placebo. Neurological and physical examinations, blood and urine analysis, ECG and EEG were performed at weekly intervals. During the entire period of phase 1, the subjects did not report any symptoms suggestive of psychotropic effect of CBD. Of the 8 volunteers receiving the placebo one gave up on the 21<sup>st</sup> day of the experiment for personal reasons; a second placebo subject reported sudoresis and “palpitations” from the 7<sup>th</sup> to the 10<sup>th</sup> day in the veins of the feet, legs, and head, stating that he had to uncover his feet to feel the palpitations less in order to sleep (Cunha, et al., p. 3). Clinical and laboratory examinations were normal and the symptoms subsided after the 11<sup>th</sup> day without any measures on the part of the investigators. Of the 8 volunteers receiving CBD, two reported somnolence, one during the first week and the other throughout the entire experiment. A third subject, with a history of mild insomnia, reported being able to sleep better during the first week of medication. Neurological and clinical examinations, EEG and ECG tracings, blood and urine analysis were within normal limits in the 16 subjects before, during, and after the experiment (Cunha, et al., p. 3). In phase 2 of the study, 15 epileptic patients, (11 female and 4 male), aged 14 to 49 years old, with a documented

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history of frequent convulsions of at least one year were selected. CBD was administered for as long as 4 ½ months (Cunha, et al., p. 8). This group was further divided based on suffering from secondary seizures and given CBD 200-300 mg/kg/day, all while patients continued to take their prescribed AED's prior to the experiment. These patients were not reacting satisfactorily to the prescribed antiepileptic drugs that they were receiving in spite of special care to assure that the patients were taking them properly. These patients had at least one generalized convulsive crisis weekly. Clinical and laboratory examinations, EEG and ECG were performed at 15- or 30-day intervals and examinations showed no signs of renal, cardiovascular, or hepatic disease. The experiment was performed in the Neurology Outpatient Clinics of the Hospital Sao Paulo (eight patients) and the Hospital da Santa Casa (seven patients) (Cunha, et al., p. 3). Each patient was followed by the same investigator, beginning two weeks before first drug administration and then throughout the whole period of drug administration. In the two weeks before CBD or placebo administration the number of focal and generalized convulsive crisis was recorded and considered as the baseline to evaluate treatment. On the first day of the experiment the patients submitted to the examinations described in phase one. They were randomly divided into one group of eight (the control group) and another group of seven (CBD group) and returned to the hospital for two more days. After one week each group received placebo or CBD capsules in a double-blind procedure in addition to the antiepileptic drugs they were already receiving. One placebo patient was transferred to the CBD group after one month. Half of each group of patients was treated in each hospital. The patients were instructed to take two or three capsules daily (containing 100 mgs of CBD or glucose) and to return to the hospital every week for clinical and/or laboratory examinations. Clinical evaluations of drug treatment was made weekly using a scale with score 0-3, which took into consideration absence of convulsive crisis or absence of

generalization and self-reported subjective improvement. According to this criterion, all patients were scored 3 during the pre-drug phase, or baseline (Cunha, et al., p. 4). It was determined that all patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. Four of the eight CBD subjects remained almost free of convulsive crises throughout the experiment and three other patients demonstrated partial improvement in their clinical condition. CBD was ineffective in one patient. The clinical condition of seven placebo patients remained unchanged whereas the condition of one patient clearly improved. CBD was found to have beneficial effect in patients suffering secondary generalized epilepsy with temporal focus, who did not benefit from traditional AED's (Cunha, et al., p. 9).

### **Online survey**

Hussain, et al. (2015) conducted an online survey in the USA, between August 8 and August 24, 2014, which included 117 parents who had administered CBD as a treatment for their children's RE's. The researchers specifically sought to recruit the parents of children with infantile spasms (IS) and Lennox-Gastaut Syndrome (LGS) patients as a means of focusing on perceived efficacy, dosage, and tolerability of CBD. The brief, streamlined survey was posted as a means of assessing basic parental impressions of the efficacy and side effects, as well as to stratify their views according to epilepsy syndromes. The study was advertised in multiple online forums including the Infantile Spasms Community ([www.IScommunity.org](http://www.IScommunity.org)) and the Lennox-Gastaut Foundation ([www.LGSfoundation.org](http://www.LGSfoundation.org)). The survey was conducted using the infrastructure of SurveyMonkey ([www.SurveyMonkey.com](http://www.SurveyMonkey.com)) and required respondents to indicate consent to participate in the study, verify that they are the parent or guardian of a child with epilepsy, and to confirm that their child received a cannabinoid product. Respondent's

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proceeded through a series of questions regarding epilepsy syndrome classification, underlying etiology, semiquantitative impression of efficacy, incidence of side effects before and after CBD exposure, and extent of CBD exposure (duration and dosage). The number of questions was minimized to reduce mid-study dropout. As a means of preventing fraudulent responses, screening of IP addresses to preclude multiple responses from a single individual and the systematic review of data to identify responses of questionable authenticity were a few of the measures taken (Hussain, et al., p. 2). Continuous summary data were presented as median and interquartile range (IQR) based on nonparametric distributions where appropriate. Unpaired comparisons of medians, and paired comparisons of medians were carried out using the Fisher exact (FE), McNemar, Wilcoxon rank-sum (WRS), and the Wilcoxon signed-rank (WSR) tests. The Bonferroni method was used to adjust for multiple comparisons. Calculations were accomplished using STATA software 9version 111, Statcorp, College Station, TX, USA) (Hussain, et al., p. 2). The vast majority of responders reported using CBD-enriched oil-based extracts, which were typically administered two to three times a day. Of the parents who knew the CBD-to-THC ratio, a great majority reported ratios of at least 15:1. Only a minority of the parents were able to provide specific CBD doses, such as exact mg/kg/day. Among 46 parents who reported patient weight and daily dosage, the median weight-based dosage of CBD was 4.3 mg/kg/day (IQR = 2.9-7.5). The median duration of CBD exposure was 6.8 months (IQR = 3.85-9.8). The perceived efficacy and tolerability were similar across etiologic subgroups regarding episodic refractory. One hundred (85%) of all parents reported a reduction in seizure frequency and sixteen (14%) reported complete seizure freedom in their children. Perceived changes in seizure frequency were typically observed quickly. 86% reported improvement or worsening within 14 days. Response patterns were similar across parent-identified epilepsy syndromes

(Hussain, et al., p. 2). Reported side effects of AED's were far less common during CBD exposure, with the exception of a 30% who reported an increase in appetite. Fifty-three percent of patients stated an improvement of sleep, 71% stated improved alertness, and 63% reported improved mood with CBD therapy (Hussain, et al., p. 2). This study is vulnerable to participation bias and had a lack of blinded outcome results. Controlled trials are needed to fully establish CBD's efficacy and safety (Hussain, et al., p. 3).

### **Online survey**

In an Australian nationwide online survey conducted between June 2016 and December 2017, Suraev, et al., (2018) inquired about experiences with the use of cannabis-based products to treat epilepsy. This study was two-fold in its approach in determining the efficacy of CBD. The first was to study the motivations and subsequent experiences of families who had used cannabis extracts in the treatment of their child suffering from "treatment resistant epilepsy" in comparison to families who were relying solely on conventional treatments. The second aim was to provide the details found when analyzing the composition and purity of the cannabis extracts in products attained by parents for this study, and if those products were perceived as "effective" or "ineffective" in the reduction of seizure frequency and noted side effects in their child from these therapies (Suraev, et al., p. 11). Also, this review aimed to make note of how these families obtained cannabinoid and the stigma, as well as consequence for these desperate parents in order to obtain and utilize cannabinoid products as a means of potential relief for their children. Semi-structured, face-to-face interviews were conducted with families of children, aged 16 or younger, who suffered with various forms of epilepsy to explore their attitudes and experiences with the use of cannabinoids (Suraev, et al., p. 2). The children's quality of life was assessed via parent report utilizing the TAPQOL and the QOLCE-55 assessment tools, which were assessed by two

different child psychologists, A.S. and R.B. Other valid assessment tools, such as The Child Behavior Checklist (CBCL), on-line questionnaires, and face-to-face interviews with families and caregivers were utilized as well throughout this study. A total of 142 parents showed interest in the study but 65 families were selected who met the inclusion criteria. Seven of those families had previously tried cannabidiol, 34 were currently using it, and 24 families had never tried incorporating it into their child's treatment plan. These families provided samples of their products for laboratory composition analysis. The purity of products obtained revealed a high variance of the chemical components of cannabinoid and seemingly revealed that the higher the percentage of THC isolate component, the less favorable the results, compared with the higher content of CBD isolate, the higher the percentage of more favorable results in reducing seizure frequency in RE patients. When parents were asked about the average change in percentages of seizure frequency since starting cannabinoids, 51% were associated with a seizure reduction of 75-100%, 10% reported a reduction of 50-75%, none fell into the 25-50% category, 4% reported a 1-25% reduction, and 20% reported no change. However, 8% reported an increase in seizure frequency, leading back to the question that the purity of the products used may have contained higher percentages of THC. One family reported complete seizure freedom for at least 12 months after the administration of cannabidiol extracts (Suraev, et al., p. 7). Survey responses were exported from REDCap electronic data capture tool and tabulated in a spreadsheet. Analyses were conducted using IBM SPSS 24.0 (IBM Corp., Armonk, N.Y., USA) and graphs were created using GraphPad Prism 7 for Mac OS X (GraphPad Software, La Jolla, California, USA). Results were summarized using descriptive statistics (frequency, percentage of valid responses). Thematic analysis was utilized to categorize open-ended responses as previously described. Responses were coded by two independent reviewers (A.S. and R.B.), before decisions

concerning the salience of themes chosen for the current research and the allocation of responses under those themes were discussed and agreement was reached. Examples of participant's responses for each theme are available in the Supplementary Methods S3. Due to the small number of families who had previously used cannabis extracts but had now stopped, data were merged to form two groups which included those who are currently or have previously used cannabis extracts ( $n = 41$ ) and those who have never used cannabis extracts ( $n = 24$ ) for their child's epilepsy. Chi-square test of significance and Fisher's exact test (two-sided) for categorical variables were used to analyze data collected during interviews. The Wilcoxon Signed-ranks non-parametric test was used when comparing two related samples. Independent samples t-tests with Bonferroni correction were used to assess differences in child's quality of life and behaviors between using and non-using families. Some families' co-administered more than one cannabis extract to their child: in this case, cannabinoid concentration data for each individual cannabis extract were merged prior to data analysis to provide a total daily dosage. An improvement in symptom control ("effective") was defined as a 1–3 on the PGIC and/or  $\geq 50\%$  reduction in seizure frequency based on the family's observation (Suraev, et al., p. 2). A non-response or deterioration in symptoms ("ineffective") was defined as a 4–7 on the PGIC and/or  $< 50\%$  reduction in seizure frequency based on the family's observation. If the family were unsure of the effects the cannabis extract was having on their child's epilepsy, such as when antiepileptic drug treatment was concurrently introduced or weaned down, the sample was excluded from the final analysis ( $n = 5$ ). The data for continuous variables were expressed as mean  $\pm$  standard deviation. Independent samples t-tests were used to compare the average cannabinoid and terpenoid concentrations between samples perceived "effective" and "ineffective". Levene's test was used to examine homogeneity of variance. An alpha level of

0.05 was used for all statistical tests (Suraev, et al., p. 3). To correct for multiple comparisons, the Benjamini-Hochberg correction was used to control the false discovery rate, with q values  $\leq$  0.05 considered significant (Suraev, et al., p. 4).

### **Retrospective cohort study**

Press, Knupp, and Chapman (2015) conducted a retrospective cohort study via chart reviews. Electronic medical records (EMR's) from 75 children and adolescent patients known to the neurology services at the Children's Hospital of Colorado who had trialed any oral cannabis extracts (OCE's) up to July 2014, for the treatment of epilepsies, and who had followed up in a single tertiary epilepsy center (Press, et al., p. 1) . Study data was collected and managed using the REDCap electronic data capture tool. The demographics included in this study were age at OCE initiation, gender, and prior established patient care, type of OCE used, seizure type, characteristics and frequency, epilepsy syndrome, adverse events, reports of benefits, and neurophysiology reports. The range of observation period was from 1 to 24 months, with the average being 5.6 months. Of the 75 patients, the parents of 43 (57%) of those 75 reported to have a reduction in seizures and were considered "treatment responders." Two patients reported to have seizure freedom at their last follow up. Eleven patients discontinued the OCE use during the study time. Seven had an adverse event, and ten did not respond. Five patients were lost to follow up while still on OCE, one of whom was considered a responder at the last follow up. Many of the families reported benefits outside of seizure frequency that included improvements in behaviors and alertness (33%), improved sleep, language (i.e., now using 3 words; 11%), and motor skills (11%), despite a limited improvement in seizures (Press, et al., p. 2) . The percentages of THC found in many of the samples appears to play a complicated roll in the assessments of these children, due to the fact that the chronic use of marijuana can lead to a

decline in cognitive function that may be irreversible. This study suggests that there is a further need to have controlled, blind studies performed to evaluate the efficacy and safety of OCE's and CBD isolate in particular (Press, et al., p. 4).

### **Internet survey**

Porter and Jacobson (2013) conducted a 24-question survey presented to parents who belonged to a Facebook group dedicated to the sharing of information regarding the use of cannabidiol-enriched cannabis as an adjunct therapy for the treatment of their children's RE. The survey was presented to one hundred and fifty members who supported the use of cannabidiol for RE patients, and with a variety of seizure types. The questions were used to measure clinical factors such as diagnosis and seizure type, as well as the parental reported effect of cannabidiol-enriched cannabis on the child's seizure frequency and side effects experienced. The survey was posted for two weeks, taken down, and then reposted again for an additional two weeks. The Stanford University institutional review board then judged the survey after study data was collected from REDCap. A total of twenty parents responded to the survey and of those responses, nineteen were found to meet the inclusion criteria of their child having been diagnosed with treatment-resistant epilepsy and for using cannabidiol as an adjunct therapy. The excluded child had not been diagnosed with epilepsy. The age of the children in the study ranged from 2-16 years old. Due to the fact that a large number of the survey results yielded positive outcomes for both seizure control and noted side effects with the cannabidiol use, the review board was then curious and decided to conduct an identical survey regarding the use of Stiripentol, a drug approved only in Europe, but which is a well-known and effective AED used to treat Dravet syndrome. Stiripentol is unrelated to other anticonvulsants and belongs to the group of aromatic allylic alcohols. It should be noted that Americans can obtain Stiripentol if so

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desired. Within this different Facebook group, which consisted of 800 members, all parents of Dravet syndrome children, the exact same survey and questions were posted for the same 2-week period, taken down, and then followed by another 2-week survey posting was performed. The study then compared the side effects from both drugs, CBD and Stiripentol. Twenty-two parents in total responded (Porter, et al., p. 3). All of the children surveyed had unsuccessfully tried an average of 12 other AED's before their parents began the CBD treatment. The amounts of THC tested and detected within the cannabinoid samples provided from survey participants were found within ranges of 0.0 to 0.8 mg/kg/day, literally only trace amounts were present. The positive results with the use of CBD were: 16/19 (84%) noted a reduction of seizures, 15/19 (79%) noted better moods, 14/19 (74%) noted increased alertness, 13/19 (68%) noted better sleep and 6/19 (32%) noted decreased self-stimulation. Conversely, the negative results with the CBD use were: 7/19 (37%) drowsiness and 3/19 (16%) fatigue. The side effects noted while taking other AED's included rash, vomiting, irritability, dizziness, confusion, and aggressive behaviors. None of those AED side effects were reported with the use of CBD. As for the results found with the Stiripentol survey: 15/22 (68%) noted reduction of their child's seizure frequency, 4/22 (18%) reported an increase in their child's frequency of seizures and 3/22 noted no changes at all in seizure frequency for their child. The noted common SE's of the Stiripentol included: 5/22 (23%) noted a decrease in appetite, 6/22 (27%) noted weight loss, 4/22 (18%) noted insomnia and 3/22 (14%) noted increased self-stimulation (Porter, et al., p. 4). Results provided high percentages of both positive and negative effects to each treatment, comparing the traditional AED to the CBD, and allowing the reader to compare a more naturopathic, alternative therapeutic plan of care for the patient.

**Retrospective study**

In a retrospective design by Porcari, Fu, Doll, Carter, and Carson (2018) to study the efficacy of artisanal CBD preparations in children with refractory epilepsies was done. Cannabis-derived products have been used medicinally since at least 2700 BCE by the Chinese and were part of the pharmacopeia in the US into the 1930's (Porcari, et al., p. 1). To determine the efficacy of artisanal CBD-containing products in the treatment of medically refractory epilepsies, the study utilized the Vanderbilt Synthetic Derivative to identify a total of 329 charts where CBD was documented out of 3,652,459 (Porcari, et al., p. 2). Two hundred and ten patients were identified, who were age eighteen years and below, one hundred and ten of which were taking CBD oil. Of these, one hundred and eight patients were documented as taking CBD oil for epilepsy, which constituted the pediatric cohort (Porcari, et al., p. 3). Given the known interactions between CBD and Clobazam, an AED traditionally used for seizures, the study group was then further divided into a subgroup to determine if Clobazam augments the beneficial effects of CBD. The response rates were also compared with CBD and Clobazam alone within an overlapping patient cohort. The addition of CBD resulted in 39% of patients having a greater than 50% reduction in seizures, with 10% becoming seizure free. The responder rate for Clobazam was similar. None of the patients achieved total freedom of seizures with the CBD used as a monotherapy, although the weaning of other AED's became possible in 22% of the patients. The most common side effect reported with the use of CBD was sedation in less than 4% of patients, all of whom were also taking Clobazam. A commonly known side effect with the use of Clobazam independently is also sedation. Increased alertness and improved verbal interactions were reported in 14% of patients in the CBD group versus 8% of patients in the Clobazam/adjunct CBD group. The benefits were markedly noted with the CBD alone group.

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The average age of onset of epilepsy within the pediatric group using CBD was three years of age, which was significantly older than the age group that were utilizing both modes of treatment, CBD and Clobazam. The most common reason for stopping the use of CBD was reported “no benefit”, whereas this was also the most common reason for stopping Clobazam (Porcari, et al., p. 3). The SE of sedation was noted more frequently with the Clobazam alone group at 36% vs 7% of patients in the CBD/Clobazam adjunct group. CBD has been reported to have many benefits other than seizure control, such as increased alertness, better social interactions and better mood, all while having very few SE’s (Porcari, et al., p. 5). While highly purified CBD awaits FDA approval, artisanal formulations of CBD are readily available and are seeing increased use by parents of this fragile patient population (Porcari, et al., p. 7). The study shows that CBD is helpful in the treatment of medically refractory epilepsy with benefits that cannot be credited to interactions with clobazam and its active metabolite alone (Porcari, et al., p. 5). These findings support the efficacy of CBD preparations in seizure reduction with few significant SE’s. The response to CBD was independent of concurrent use of Clobazam, although the Clobazam may have contributed to the sedation seen with the concurrent use of CBD (Porcari, et al., p. 3).

### **Randomized double blind placebo controlled trial**

Thiele, et al. (2018) conducted a randomized, double blind, placebo-controlled phase 3 trial conducted on patients with Lennox-Gastaut Syndrome (LGS). LGS is a rare and severe form of epileptic encephalopathy, with an early childhood onset, which is frequently known to be treatment resistant to available AED medications. The syndrome typically manifests by eight years of age with peak incidence between the ages of three to five years old. No controlled studies have investigated the use of cannabidiol for patients with seizures associated with LGS;

therefore, this particular study was conducted to assess the efficacy and safety of CBD as an adjunct therapy in this particular patient population (Thiele, et al., p. 1). This study was conducted at 24 different clinical sites around the United States, Netherlands, and Poland. Eligible patients for this study happened to be selected in age ranges from 2-55 years old (Thiele, et al., p. 2). LGS is a lifelong condition that leaves 20-60% of patients with cognitive delays at the age of disease onset, leaving 75-95% of patients becoming more cognitively impaired with age, and therefore makes robust studies of adjunct CBD challenging. Between April 2015 and October 2015, a total of 171 randomly assigned patients were selected to either receive a starting dose of 2-5 mg/kg/day and gradually increasing to 20 mg/kg/day of pharmaceutical grade, purified CBD oil or “look alike” placebo oil in identical vials (Thiele, et al., p. 5). A data safety monitoring committee was used to monitor ongoing patient safety during the trial, as well as an adjunct committee was utilized to monitor for potential signals of abuse or misuse during the study. All patients received treatment for 14 weeks, which included 2 weeks of dose escalations. Patients were assessed in the clinic on days 15, 29, 57, and 99 and also by telephone on days 43 and 71 (Thiele, et al., p. 3).

Any patient who tested positive for tetrahydrocannabinol (THC) at the beginning of the study was considered ineligible and dropped from the study cohort (Thiele, et al., p. 2). The median percentage of reduction in monthly seizures from baseline was 44% in the CBD group and 21.8% drop in the placebo group. Significantly more patients in the CBD group compared to those in the placebo group achieved reductions of 25% or more or 75% or more in monthly frequency of drop seizures from baseline during the treatment and maintenance periods. None of the patients were free of drop seizures throughout the entire 14 week treatment period, but three patients in the CBD group who completed treatment were drop seizure free throughout the

twelve week maintenance period (Thiele, et al., p. 5). A drop seizure was defined as an attack or spell (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that lead or could have led to a fall, injury, slumping in a chair, or hitting the patient's head on a surface (Thiele, et al., p. 3). Adverse effects were noted in 86% of the patients in CBD group vs 69% reported in the placebo group. The most common adverse effects reported were diarrhea, somnolence, fever, decreased appetite, and vomiting (Thiele, et al., p. 5). Generally, with RE patients, they are already taking at least two AED's and have been found to still be refractory with many other traditional AED's, all of them known to have similar and more life threatening potential side effects. Nonpharmacological treatments such as a ketogenic diet, vagus nerve stimulation, or resective surgeries have also been incorporated into the treatment plans for these patients yet less than 10% of them become seizure free with existing treatments. Adjunct CBD has been proven as efficacious for the treatment of RE patients with LGS, as well as with Dravet Syndrome, among others, and is generally well tolerated (Thiele, et al., p. 11). This study took its statistical information from various geographic regions, from a variety of ages, and while being monitored by several committees simultaneously, such as US Food and Drug Administration (FDA), the European Medicines Agency, and an independent committee of experts from the Epilepsy Consortium (Thiele, et al., p. 3). The long term efficacy and safety of CBD is currently being assessed in an open-label extension of this trial.

### **Expert opinion-multiple studies**

Leo, Russo, and Elia (2016) presented an expert opinion, which included the clinical evidence of ten studies done on CBD and its use as a treatment for RE. Some examples of those studies include: one study performed with 310 outpatients, from a tertiary epilepsy center in Berlin, where these patients were evaluated and found that the incorporated use of CBD did not

worsen epilepsy, in contradiction with what has happened after some patients abused other illicit drugs. Another retrospective study performed in Colorado of 75 children and adolescents who have been administered oral cannabis extracts for the management of their epilepsy, where 57% of those parents attest reduction of their children's seizures by approximately 50% was reviewed (Leo, et al., p. 5). Despite the introduction of new AED's constantly on the frontier of attempted relieve for the fragile population of pediatric patients suffering with these spontaneous reoccurring seizures, epileptogenesis remains a scantily understood cascade of events. As of yet, both the newer and the older AED's have not improved the outcome of RE, and they demonstrated several intimidating side effects which influenced the quality of life just as much as the seizures themselves (Leo, et al., p. 1).

The pharmacological interest in cannabis compounds arose after the identification of two major neuroactive components: psychotropic THC and non-psychotropic CBD, as well as after the discovery of an endogenous cannabinoid-signaling pathway. CBD, the second most abundant phytocannabinoid extracted mainly from cannabis sativa and cannabis indica, has demonstrated antiseizure activity and a good side-effect profile. CBD has also been suggested to exert antipsychotic, antidepressant, and anxiolytic properties, and CBD's effects on cognitive functions as well as mood might be useful considering epilepsy comorbidities, which represent an important issue in the management of epileptic patients (Leo, et al., p. 2). Phytocannabinoids have been medicinally used to treat neurological disorders and epilepsy for centuries. Of note, most Phytocannabinoids do not act on the endocannabinoid system, as is the case with CBD. In preclinical "in vivo" studies, CBD has shown significant anticonvulsant effects within acute animal models for seizures, whereas there is restricted data within chronic human and animal models of epileptogenesis (Leo, et al., p. 2). Clinical evidence has repeatedly indicated that CBD

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is effectively able to manage epilepsy in both adults and children that are affected by RE seizures and with a favorable side effect profile in comparison to currently applied AED's. Likewise, CBD, in animal models, has also demonstrated effects on cognitive performance as well as in mood disorders. Only double-blind, placebo-controlled, randomized clinical trials in which consistent preparations of CBD are used to treat patients with homogenous and well-defined epileptic syndromes may provide reliable, scientific, and evidence-based information on efficacy and safety of CBD, in order to influence the current restrictive regulatory laws in many countries in the world and accelerate its legal use in clinical practice (Leo, et al., p. 7).

### Matrix of studies reviewed

Author, Year Published, Country	Study Design and sample size	Sample characteristics and method	Results	Conclusions
Aguirre-Velazquez (2017) Mexico	Structured online surveys of parents w/RE children using CBD, 53 cases selected	43 cases were from Mexico, 10 from other Latin American countries; 47% had been previously treated with 9 or more AED's	81.3% reported a decrease in seizures, 51% w/a moderate to significant decrease, 16% were free from seizures. The # of AED's used was reduced in 20.9% of cases	No serious side effects were reported, with only some mild adverse effects such as increased appetite or changes in sleep patterns reported in 42% of cases. These parents would classify CBD as useful as adjunct therapy for RE children. Clinical protocols in large centers where there are high numbers of RE patients still need to be determined
Cilio et al. (2014) USA	Expert opinion, literature review regarding the incorporation of CBD as an adjunct therapy along with multiple ARD administration	Statistics taken from a recent U.S. survey conducted on 19 parents of RE pediatric patients, 12 with DS	Of parental responses 53% report >80% reduction in seizure frequency, 11% were seizure free during a 3 month trial of incorporating CBD into the AED medication	Significant decrease with RE's, including those with DS. Reports of improved alertness and none reported severe side effects, a few reported drowsiness and fatigue. The U.S. greatly needs to consider lifting the Schedule 1 CSA classification, along with federal prohibitions and

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			regimen. Among the 12 DS patients, 42% report >80% reduction	educational stigmas
Cunha et al. (1980) Brazil	Double blind placebo setting with 16 healthy human volunteers	<p>For 30 days of Phase 1, 8 volunteers were given 3 mg/kg/day of CBD and the remaining 8 were given a placebo. Neurologic and physical exams, blood and urine analysis, ECG and EEG performed at weekly intervals.</p> <p>CBD was administered for as long as 4 ½ months. These groups were further divided based on suffering from secondary seizures and given 200-300 mg/kg/day, all while patients continued to take their prescribed AED's prior to experiment knowing they were unsuccessful at controlling disease</p>	All patients and volunteers tolerated CBD very well and no signs of toxicity of serious side effects were detected upon exams. 4 of the 8 CBD patients remained almost free of convulsions. CBD was ineffective in 1 patient. The condition of 7 placebo patients remained unchanged, 1 placebo patient clearly improved	CBD was found to have beneficial effect in patients suffering secondary generalized epilepsy with temporal focus, who did not benefit from AED's. Further research with more patients and other forms of epilepsy are needed to establish the scope of the antiepileptic effects of CBD in humans
Devinsky et al. (2017) USA	Double-blind, placebo-controlled trial of 120 Dravet Syndrome and drug resistant pediatric RE patients	Randomly assigned to receive either CBD at a dose of 20 mg/kg/day or placebo, in addition to standard AED treatment over a 14 week period	The % of patients w/a least a 50% reduction of seizure frequency was 43% with CBD & 27% w/placebo. The % of patients who became seizure free was 5% with CBD, 0% with placebo	Among patient's w/Dravets Syndrome, CBD results in a greater reduction of convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. Further studies are needed to compare these adverse events with those of traditional AED's

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Fasinu, Philips, ElSohly, and Walker (2016) USA	Position statement including 54 studies where CBD was used to measure treatment outcomes of drug-resistant seizures and disorders	Currently registered clinical trial of CBD. Studies based on condition, # of trials, age of patient, results, formulation and dosage, & route of administration	Reductions noted in the frequency of seizures and the # of adverse effects experienced for patients	Judging so far, CBD has great potential utility, but uncertainties remain regarding sourcing, long-term safety, abuse potential and regulatory dilemmas
Geffrey, Pollack, Bruno, and Thiele (2015) USA	Investigational New Drug trial (IND), total of 25 patients, 13 being treated w/Clobazam (CLB) and CBD simultaneously	Subjects and caregivers were interviewed either in person, over the phone, or emailed. 13 of the 25 children studied were being treated with CLB and having varied side effects. Throughout the study CBD dosing was either decreased (w/SE) or kept constant and blood levels drawn and analyzed over a 4-8 week study	9/13 patients had a > 50% decrease in seizures, corresponding to a responder rate of 70%. The mean change in seizure frequency was a 51% decrease by 56%. Only 2 patients had an increase in frequency (14%) and both of these patients had a decrease in their CLB dose over the course of CBD adjunct treatment	There is a drug-drug interaction noted w/CLB and CBD when metabolized; reduction of CLB dose alleviates consequential SE's & all subjects continued to tolerate CBD well throughout trial. CBD appears safe & effective in pediatric patients on CLB treatment for RE's
Hussain et al. (2015) USA	Online survey of 117 parents who administered CBD for treatment of their children's RE's	53 of those children w/IS or LGS, perceived efficacy and tolerability were similar across subgroups of refractory	85% of all parents reported a reduction in seizure frequency and 14% reported complete seizure freedom.	Reported side effects of AED's were far less common during CBD exposure, with the exception of a 30% increase in appetite. 53% state improvement of sleep, 71% state improved alertness, 63% report improved mood with CBD therapy. This study is vulnerable to participation bias and limited lack of blinded outcome ascertaining. Controlled trials needed to fully establish efficacy and safety.
Koppel et al. (2014) USA	Systematic Review of 34 studies, 8 rated as Class I. Of the 1,729 abstracts reviewed, 63 full texts articles found that 33 met criteria. an updated search in 2013 yielded 1 article for	From 1948 to 2013 evidence-based reviews of seizure frequency and symptom treatment with CBD for epilepsy, CBD being isolated in 1963	The concentration of THC present in formulations & the ratio of THC to CBD, which limits the psychoactive effects, play a role in therapeutic effects of Cannabis products	There were no Class I-III studies, there were 2 Class IV studies that did not demonstrate significant benefit and did not show adverse effects over 3-18 weeks of treatment. Further research with randomized controlled studies is necessary in order to determine the efficacy of this medication class

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	inclusion			Schedule 1, which may be difficult due to the stigma and additional burden placed on researchers in the USA
Leo, Russo, and Elia (2016) Italy	Position statement including 10 studies where CBD was utilized both in vivo and in vitro as a means to study epileptogenesis and the signaling pathways of cannabinoids	Periodic case reports of infant children timespan from 2 weeks to 1 year, parental survey of 117 & Face Book survey, retrospective case study of 75 & 74, prospective/ placebo controlled trial with 15 and 12 & 9, prospective-randomized-double blind placebo-controlled trial of 12, multicenter open-label trial of 214 patients aged 1-30.	50% reduction in seizure frequency reported in up to 89% of patients, up to 50% becoming seizure free, only 1 patient reports no significant reduction.	Patients have become more alert and able to maintain oral nutrition, parents state they have a "new child", better mood affect noted, improved language and enhanced motor performance, parents feel as through CBD has a better safety profile and less consequential SE's when compared to AED's. Drowsiness and mild GI upset noted w/CBD to be equivalent for many patients when compared with AED's.
Porcari, Fu, Doll, Carter, and Carson (2018) USA	Retrospective cohort study of 108 pediatric refractory epilepsy patients	Samples were collected from medical records over a time frame of 2006-2016, using keywords of CBD	The addition of CBD with Clobazam resulted in 39% of patients having a >50% reduction in seizures, with 10% becoming seizure free	These findings support the efficacy of artisanal CBD preparations in seizure reduction with few significant side effects. The response to CBD was independent of concurrent use of Clobazam, but Clobazam may contribute to the sedation seen w/concurrent CBD use
Porter and Jacobson (2013) USA	Facebook survey from 2 groups of parents with children ages 2-16, diagnosed with RE's and having used either traditional AED's and/or CBD. 1st survey 20/150 eligible responses and	Facebook group posted 24 question survey to 150 members with RE children who have trialed CBD, 19 eligible responses and identical survey posted to different Facebook group of 800 members, whose	CBD use: 16/19 (84%) decrease in seizures, 2/19 seizure freedom, 8 reported > 80% reduction in frequency, 3 reported > 50% reduction of frequency, & 3 reported > 25% reduction in	When CBD surveyed alongside Stiripentol, an AED successfully used & available only in Europe, statistics reveal that the CBD was more effective than the AED at reducing seizure frequency and with having a > amount of positive side effects while having a < amount of negative side effects than

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	the 2nd survey 22/800 eligible responses	RE children have trialed up to 12 traditional AED's, 22 eligible responses. Each posted for a total of 4 (2+2) weeks	frequency. 3/19 report no changes. 12/19 parents weaned their child from another AED after starting CBD	compared with the use of the traditional AED
Press, Knupp, and Chapman (2015) USA	Retrospective chart review of 75 children and adolescents who were given Oral Cannabis Extracts (OCE) for treatment of epilepsy	Data was extracted from EMR's and entered into database by OP, IP, telephone, & email, then reviewed including demographics, seizure characteristics, frequency, AE's, type of OCE used & dosing, reports of additional benefits, and neurophysiology reports	43/75 reported improvement in seizures, 25/75 had > 50% reduction in seizures, 2/75 reported seizure freedom; responder rate varied based on epilepsy syndrome	OCE used demonstrates that some families reported improvement. There was a variety of challenges & possible confounding factors. Studies suggest that the % of THC in OCE products plays a large part in altering test results of efficacy. CBD isolate shows promise and should be further investigated
Suraev et al. (2017) Australia	Nationwide online survey of experiences with CBD for epilepsy treatment; 976 respondents met inclusion criteria; survey was posted for 10 days	39 questions assessing demographics, clinical factors of diagnosis, seizure type, past treatment w/AED's	15% of adults w/epilepsy and 13% of parents w/epileptic children currently using or have used CBD as adjunct therapy; of those 90% of adults & 71% of parents report success in reducing seizure frequency	Almost ½ of the respondents w/a history of CBD use report a reduction in the amount of AED's used after the initiation of adjunct CBD therapy. The # of past AED's tried was a significant predictor of CBD use in both adults & children w/epilepsies. RE's & dissatisfaction w/the side effects of AED's were the 2 main reasons for trying CBD. Further studies warranted regarding knowledge of efficacy, safety, and potential treatment
Suraev et al. (2018) Australia	Face to face, semi-structured interviews with 65 families of RE patients who have tried, are using, or have never used Cannabinoid as an adjunct therapy	7/ 65 families had previously used, 34/65 were currently using, and 24/65 had never used as an adjunct therapy	51% claim seizure reduction by 75-100% in frequency; 10% claim reduction of 50-75%, none claim a reduction of 25-50%, 4% claim reduction of 0-25%, 20% claim no change, and 8% claim an increase in seizures	The purity of products must be validated as having only trace elements of THC vs the highest % element being CBD. These products should be regulated by the FDA and more extensive studies should be conducted into the incorporated use of CBD as either an adjunct treatment of a sole treatment option for RE patients & their parents.

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<p>Theile et al. (2018) USA Netherlands Poland</p>	<p>Randomized, double-blind, placebo-controlled phase 3 study, done in 24 clinics, of 171 patients ranging in age from 2-55 years old</p>	<p>All eligible patients had LGS had a history of seizures for at least 6 months, at least 2 drop seizures per week during the 4-week baseline period, and has not responded to at least two (2) AED's. All patients received either CBD or placebo in identical 100 mL amber glass vials that could not be visibly</p>	<p>The median % of reduction in monthly drop seizures was 43.96% in CBD group vs 21.8% reduction in the placebo group. Adverse effects were similar in rates to traditional AED's when compared to CBD and placebo groups</p>	<p>Adjunct CBD is effective for the treatment of patients with RE and is generally well tolerated</p>
<p>Tzadok et al. (2016) Israel</p>	<p>Retrospective Cohort Study of 74 patients w/RE resistant to &gt; 7 AED's</p>	<p>5 Israeli pediatric epilepsy clinics treating children and adolescents (ages 1-18) diagnosed as having RE with a regimen of medical CBD. Study divided patients into 6 groups based on seizure etiology</p>	<p>CBD yielded a significant positive effect on seizure load. 89% report reduction in seizure frequency, 18% w/75-100% reduction, 34% w/50-75% reduction, 12% w/25-50% reduction. 5% report aggravation of seizures</p>	<p>Improvement of behavior and alertness, language, communication, motor skills, and sleep. Adverse effect w/somnolence, fatigue, GI upset, and irritability, which lead to withdrawal of CBD in medication regimen. Well-designed clinical trials are further warranted</p>

### **Chapter 3: Methodology**

This study used integrative literature review as a means of supplying the building blocks to construct nursing science, to integrate informative research from healthcare providers and experts alike, and to assist in the theory development, which has direct applicability to the practice and policies of this highly controversial adjunct therapy of a cannabis derivative used for children. The design for this project is best suited for an integrative literature review as an attempt to (1) summarize past theoretical literature and (2) provide insight into the marginal research yet performed regarding the keen benefits of isolated CBD use for the intensely vulnerable population of pediatric patients diagnosed with rare and refractory epilepsies (RE). There are five stages to accomplish these two goals: (1) problem identification, (2) literature search, (3) data evaluation, (4) data analysis, and (5) presentation (Whittemore & Knafl, 2005).

#### **Problem Identification**

As a means of problem identification, it is noteworthy to point out, that despite the availability of more than 20 prescription strength antiepileptic drugs (AED's) in the US, these conventional treatment options have proven ineffective in approximately 25-30% of epileptic patients (Suraev et al., 2017). Resistance to traditional treatment options is well defined in many studies from randomized controlled trials, surveys, and cohort studies, making it a prime area of research for the adjunct therapy option of cannabidiol (CBD). Ironically, the use of cannabis is not new in the eyes of scholarly research. According to Dr. Daniel Friedman and Dr. Orrin Devinsky, cannabis has been used medicinally for millennia and was used in the treatment of epilepsy as early as 1800 B.C.E. in Sumeria. Victorian-era neurologists used Indian hemp to treat epilepsy and

reported dramatic success. The use of cannabis therapy for the treatment of epilepsy diminished with the introduction of phenobarbital in 1912 and phenytoin in 1937 and the passage of the Marijuana Tax Act in 1937. The discovery of an endogenous cannabinoid-signaling system in the 1990's rekindled interest in therapies derived from the constituents of cannabis for nervous stem disorders such as epilepsy (Friedman & Devinsky, 2015). However, the lack of evidence regarding the medical potential for CBD has largely been due to the societal attitudes toward cannabis and the fact that it is still classified as a Schedule 1 drug within the US and thus poses huge obstacles for research (Cohen, 2017, p. 5).

For millennia, cannabis has been utilized by physicians and patients. Cannabidiol (CBD) provides a highly beneficial pharmacologic effect, which is the non-psychoactive compound, when isolated and derived from the cannabis plant. Cannabis has been known, and used, as one of the oldest psychotropic anticonvulsants. For the past few years several studies have started surfacing as a means to validate CBD and its use as an adjunct therapy for pediatric patients with drug resistant seizure disorders and rare refractory epilepsies (Verrotti, Castagnino, Maccarrone, & Fezza, 2016). Therefore, the concept of delving into the study as a genuine means of adjunct therapy most certainly qualifies for the need of future research.

### **Literature Search**

The following databases were searched for this study: PubMed, PubMed Central, CINAHL, Cochrane, Google Scholar, several Medical Journals and several University Libraries. The key words CBD, cannabidiol, children, medical cannabis, anticonvulsant, intractable epilepsy, refractory epilepsy, side-effects, treatment resistant, and healthy

volunteers were used, In addition, various methods of data collection were reviewed which included, randomized controlled trails, cohort studies, surveys, physician and expert authorities regarding observational studies, systematic reviews, and physiologic and procedural studies. By continuing to focus on the pediatric epilepsy aspect of CBD benefits, 12 solid articles of mixed studies were found and another 10 physician and expert opinions articles were reviewed.

### **Data Review**

The final data evaluation samples for this integrative literature review included expert position statements, retrospective cohort studies, structured and nationwide online surveys, investigational new drug (IND) trials, double-blind placebo-controlled trials, and systematic reviews. Due to the varied illustrations found within the primary resources, much of the data represented was found to be relevant in its methodological and theoretical approach, as far as comparing the patient outcomes of utilizing CBD for pediatric RE patients. My search for higher evidential design for cause-probing research questions will continue.

### **Data Analysis**

Data analysis was extracted from 16 initial primary resources, which were based on sample characteristics from a variety of data extrapolations, as well as from an additional 31 expert opinions, which were a compilation of varied research studies. Categories that were extracted included an integration of studies that compare the patient outcomes of integrating CBD into the medication regimen of highly compromised RE pediatric patients rather than continuing with unsuccessful polypharmacy traditional

AED's. As far as the vast majority of scholars have discovered, the potential for successful attempts far outweigh the outcomes of continued unsuccessful therapy options.

### **Presentation**

The presentation of this thesis comes from a comprehensive model as a means to portray the benefit versus the risk of incorporating CBD for pediatric patients whom have been suffering with refractory epilepsies. As studies continue to climb to the forefront of research, this topic will remain a "hot issue" seeing as the US federal and state laws remain in controversy over the legalization of medical cannabis and its beneficial chemical components.

## Chapter 4: Results

The researcher explored a total of 47 articles for this study, 16 were selected for analysis for this literature review. The overall analysis for building a case for CBD as being safe and effective as an adjunct therapy for children with refractory epilepsy (RE) is astonishing. The qualifying factor for inclusion within studies were that children needed to have attempted prior AED's in excess of three to twelve different AEDs in variation, while remaining uncontrolled with seizure activity on AED's alone, or while taking multiple AED's at once. Included within this research were the numerous undesirable, and at times life-long, side effects incurred by traditional AED's. The research has been compiled over a time period from 1980 through 2018, a span of over three decades, 38 years in total. Research was located dating back to 1948, and researcher discovered that CBD had started being isolated as a cannabinoid back in 1963. The research was located from areas such as Jerusalem, United States of America, Israel, Mexico and other Latin American countries, Australia, Netherlands, Poland, and Italy. Research included in this thesis encompassed cohort studies, in-vivo and in-vitro studies of both animal and human children, parental/care-giver surveys, multiple Face Book surveys with children studied ranging in ages from 2-16, retrospective studies, prospective studies, placebo controlled trials, randomized double-blind controlled studies, multi-center open-label trials of patients aged 1-30 years old, face-to-face semi-structured interviews of 65 families, controlled phase 3 studies of 171 patients aged 2-55 years old, structured on-line surveys with 53 selected patients, medical records search, patient chart reviews, systematic review of Class 1 drug studies of 34 concurrent trials, a 10-day nationwide on-line survey of 976 patients trialing cannabidiol use, and an investigational

new drug (IND) trial of 25 patients with 13 of them on Clobazam simultaneously. The response rates consistently remained favorable, lying anywhere between 50% to 89% for a reduction in the frequency of seizure activity within a pediatric population, and even more so within the adult population of RE patients, that number remained at approximately 90%, just to keep a frame of reference within the research. A reduction in the number of traditional AED's used while adjunct CBD was administered remained at approximately 21%. An average of 51% noted a "moderate to significant" reduction of seizure frequency, approximately 20% noted seizure frequency to drop by 75-100%, and 15% noted a drop in frequency by 25-50%. Between 5-8% noted in various studies to see an increase in seizure activity, however the ratios of THC to CBD were also noted to be higher within the cannabidiol samples retrieved from that studies population, and subsequent adjustments were made to their dosing of CBD administration. Averages of 16-19% in other studies claim that patients became seizure free while taking adjunctive CBD preparations. An average of 12/19 parents within one study claim that they were able to wean their RE child off of at least one traditional AED by supplementing with CBD into the daily medication regimen. Apparently, the THC to CBD ratio of purity found within samples played a role in the studies conducted, as THC does in fact have a psychoactive quality, to where CBD has zero psychoactive or addictive quality to it. This factor made a difference in the outcomes of therapeutic effect and for potential aggravation of seizure activity within the pediatric population. The purity of products certainly must be verifiable by the parents and care takers of this population. Only 1% of population samples noted CBD to be ineffective for seizure reduction in their child. Ironically, within the placebo groups studied, anywhere from 1-7% noted an

## CBD AS AN ADJUNCT THERAPY FOR RE CHILDREN

improvement as well in seizure activity. Across the board within all studies, the side effects noted while utilizing CBD as an adjunct therapy while taking AED's were the same, no increase was noted with any mild to moderate SE's of sedation and GI upset. However, with traditional AED's the SE's are noted to be life threatening and long-term regarding cognitive and hepatic functions. It also was noted that the type of epilepsy diagnosis and the severity played a factor in the studies as well, and that the more serious types are far less frequently diagnosed within the pediatric population, those being Lennox Gastaut Syndrome (LGS) and Dravet Syndrome (DS), to name a couple. Clobazam, a traditional AED, was noted in many studies to work well with CBD as an adjunct therapy, and many studies noted that the dosing amount was successfully decreased due to the addition.

## **Chapter 5: Discussion and Recommendations**

The purpose of this study was to determine the safety and efficacy of utilizing CBD as an adjunct therapy, alongside or potentially in place of traditional AED's, used for decades with refractory epileptic (RE) pediatric patients. This fragile and rare population continues to require much needed research into how the medical world can offer relief or even a cure for these unrelenting and life altering recurrent seizures. In studying the possibility of incorporating CBD into the medication regimen, studies have found that there is genuine potential for this with cannabinoids. Study after study corroborates that children have had a significant and welcome change in the quality of life in regards to improved behaviors, better mood and overall affect, increased alertness, improved language and communication skills, enhanced motor skills and better motor performance, healthier changes in sleep patterns, increased appetite and increased tolerability to maintain oral nutrition, and an overall better safety profile noted by parents when compared to traditional AED's. The noted SE's were less with AED's once CBD exposure occurred. The same noted side effects of AED's were also recorded and noted with CBD use, those being somnolence, fatigue, mild to moderate GI upset, and irritability. Some recommendations for the incorporation of CBD alongside traditional AED's used would be to verify the purity of artisanal cannabinoids used, the ratio of THC should be trace in comparison with the ratio of CBD being the largest, by far, contained within the product choice. In various studies, Clobazam (CLB) and CBD show a favorable drug/drug interaction noted when metabolized, and the ability to decrease the dosing milligrams of CLB was noted to help decreased any noted SE's when medications were taken simultaneously.

**Recommendations for further research**

This study has been an ongoing health concern and challenge for decades. Until quite recently, strict state and federal regulations have been a stumbling block for many states within the United States. Drug scheduling from the Controlled Substance Act (CSA) of 1970, which is federally regulated, has yet to relinquish “Marijuana,” or any cannabinoid constituents, as anything less than a “Schedule 1” drug alongside Ecstasy, LSD, and Heroin, to name a few. Even Cocaine and Morphine remain at a Schedule 2 category, despite mountains of medical research done regarding the use of CBD’s use medicinally to aid in a multitude of disease and illness issues (Cohen, 2017, p. 5). It is highly recommended that both parents and health care advocates continue to fervently research the use of CBD as an adjunct therapy for RE patients and that both health care advocates and parents alike continue to propose regulatory lifts on Schedule 1 class Marijuana, CBD in particular, as a means of continued research and life changing aid for this vulnerable patient population that are yet to attain seizure control, in spite of the administration of several AED’s used simultaneously that evoke a multitude of undesirable side effects.

**Limitations**

Due to the scarcity of blinded control trials within the pediatric population and the rarity of these refractory epilepsies, as well as the rigid CSA regulations regarding the prescribing of cannabinoids as a Schedule 1 medication, prescriber’s knowledge regarding the efficacy and safety of CBD remains an area of limited research. The studies located were therefore limited to participation bias, as these parents and caregivers are just as vulnerable as the children being exposed to the devastation of unrelenting seizures,

as well as to a dramatically lower quality of life. The limited lack of blinded, controlled trials remains to be an issue, although the use of CBD is hugely on the frontier of medical research and trials that are now under way. There are at least 37 studies currently under way and those can be located at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Further research articles will no doubt be published and will include an increased number of patients with various forms of RE's. These studies are much needed to establish the scope of the antiepileptic effects of CBD in humans.

### **Conclusions**

Cannabidiol has a wide range of biological effects with multiple potential sites of action within the nervous system. Plenty of preclinical evidence for antiseizure properties and a favorable side effect profile support further development of CBD based treatments for epilepsy.

The safety and efficacy of CBD has thus been well proven within the literature that the researcher has reviewed. According to local neurologist, Dr. Loveneet Singh, (personal communication, May 13, 2016) he indicates that, per his professional experiences, "CBD has remained a safe and advantageous adjunct therapy for RE patients, but it is still thought that it should not to be used in a fashion to where parents and patients are under the impression that it should be used as a monotherapy for RE patients due to the potential of worsening seizures for the child should therapeutic levels of AED's be abruptly discontinued. The administration of CBD and any weaning of traditional AED's should continue to be monitored by the prescribing MD". Pediatric populations in this study are vulnerable and need to have strict governance over trials and

medication administrations, therefore well-defined and well controlled studies should continue to progress forward.

The FDA now has approved the use of Epidiolex, a CBD cannabidiol, and it will be legally used to treat Lennox-Gastaut Syndrome and Dravet Syndrome. Epidiolex is the first approved CBD treatment for LGS and DS (Price, 2018). Artisanal forms of CBD can be purchased legally in various forms. Because CBD from hemp has no psychoactive effects, the purchase, sales, or possession of hemp CBD products are completely legal in all 50 States. Because hemp is sometimes confused with the marijuana plant, there is still some stigma towards hemp-derived CBD, but from a legal perspective, hemp-derived CBD is completely legal and enjoys the rights of any other legal product (Cadena, 2018).

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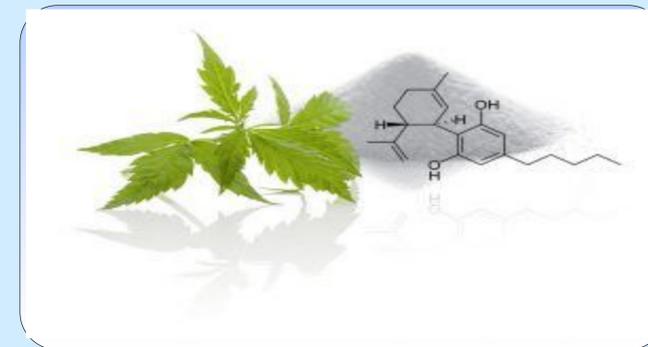
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# THE USE OF CANNABIDIOL (CBD) AS AN ADJUNCT THERAPY FOR REFRACTORY EPILEPSY (RE) CHILDREN

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## Introduction

Severe epilepsies of infancy and early childhood are chronic conditions characterized by recurrent, unprovoked seizures and developmental delays. Worldwide, approximately 17.5 million people have been diagnosed with treatment resistant RE's which frequently requires the use of polypharmacy. Treatment resistant is defined as a failure of 2 appropriate trials of AED's (alone or in combination) to achieve seizure freedom, in attempts to curb the debilitating seizure episodes and mounting side effects (Suraev, et al., 2018).

Nearly 2.4 million new cases are diagnosed annually according to the World Health Organization (Megiddo, et al., 2016).

CBD has a highly beneficial, non-addictive, non-psychoactive pharmacologic effect when this compound is isolated and derived from the Cannabis plant, and has been used for centuries as one of the oldest anticonvulsants. For several years, studies have surfaced as a means to validate CBD and its use as an adjunct therapy for pediatric patients with drug resistant seizure disorders and rare refractory epilepsies (Verrotti, Castagnino, Maccarrone, & Fezza, 2016).

State and federal government have been undergoing a tremendous amount of pressure to legalize the use of cannabis and/or its derivatives for medical purposes. CBD exhibits neuroprotective, antiepileptic, anxiolytic, antipsychotic, and anti-inflammatory properties (Fasinu, Phillips, EISOhly, & Walker, 2016).

## Methods

16 articles reviewed included: met analysis, retrospective cohort studies, investigational new drug trials, nationwide online surveys, randomized double-blind placebo-controlled trials, systematic reviews, and expert opinions. All of which selected patients based on age, diagnosis, polypharmacy use, seizure frequency, side effect profiles, and the child's quality of life.

Databases searched for this study: PubMed, PubMed Central, CINAHL, Cochrane, Google Scholar, Medical Journals and University Libraries, while using the key words of CBD, cannabidiol, children, medical cannabis, anticonvulsant, intractable epilepsy, refractory epilepsy, side-effects, treatment resistant, and healthy volunteers.

Figures 1 and 2 illustrate the effects on seizures and the effects of quality of life factors (Aguirre-Velazquez, 2017).

Figure #1

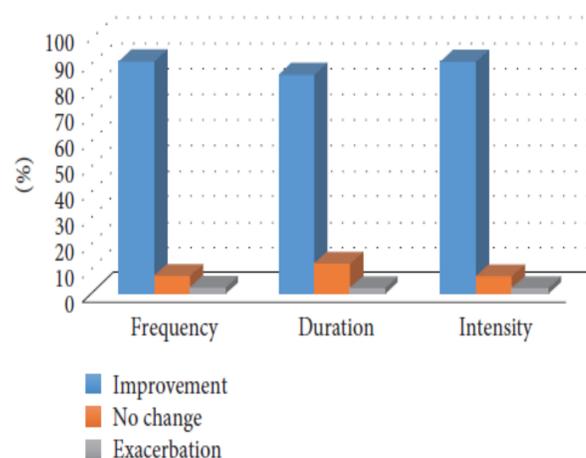


FIGURE 1: Effect of treatment with CBD on convulsive seizures.

## Results

In all of the studies conducted, CBD was found to decrease seizure frequency by approximately 50-90%, and of those patients, approximately 16% became seizure free. This allowed parents to wean their children off of traditional AED medications and to decrease the potential side effects from AED's once CBD was incorporated into the medication regimen.

Noted SE's of AEDs are: drowsiness or difficulty sleeping, dizziness, suicidal thoughts or actions, emotional depression, respiratory depression, electrolyte imbalance, dependence and inability to withdraw, multiple organ issues, urinary retention, blood disorders, hyperactivity, weight gain or weight loss, gastric issues, birth defects, memory loss, tremors, agitation, worsening of seizures, hair loss, vision problems, and metabolic acidosis (Leo, Russo, & Elia, 2016).

Figure #2

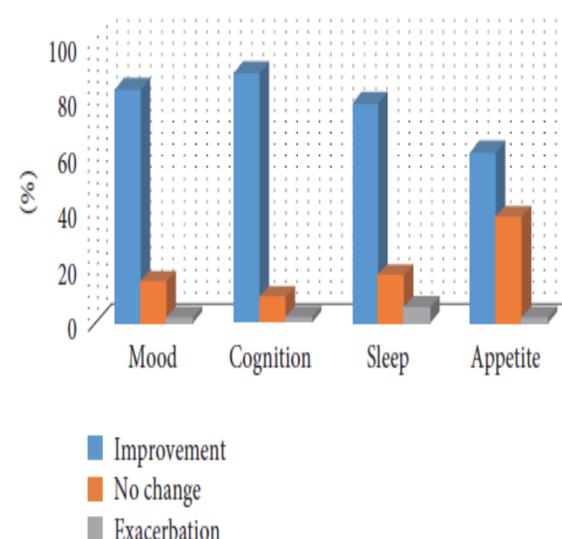


FIGURE 2: Effects of cannabidiol on quality of life factors.

## Conclusions

The results of these studies indicate that CBD is highly useful as an adjunct ("add on") treatment for RE children, as it significantly reduces the frequency, duration, and intensity of seizures. It also improved aspects of the patients' quality of life in terms of their emotional and cognitive states, sleep patterns, better mood and affect, improved language, enhanced motor skills, improved dietary intake, and a healthier safety profile. There was an absence of serious adverse effects, with only some tolerable mild adverse effects experienced with CBD based treatment. Parents noted drowsiness and mild GI upset to be equivalent when compared with AED's side effect profile when CBD was incorporated (Leo, Russo, & Elia, 2016).

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