AN EVALUATION OF EFFECTIVENESS OF CANNABIDIOL AS AN ANTIEPILEPTIC DRUG FOR CHILDREN WITH INTRACTABLE GENERALIZED EPILEPSY

By

CHRISTOPHER LOGAN ANDERSON

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2017

To my parents, Mark and Debra Anderson, whose love and unselfish support guided me through this journey and prepared me for the next

ACKNOWLEDGMENTS

I would first like to thank my family and friends for all of their support throughout the years and for encouraging me to not only pursue my dreams but to accomplish them. Without all of these people in my life this opportunity would not have been possible. I would like to especially thank my advisor, Dr. Paul Carney, for seeing the potential in me as a student and colleague and helping me become the best researcher I could. His support and dedication to this study, our research, and my successful graduation has never waivered and for that I could not be more grateful.

Thank you to my committee members, Dr. Brandi Ormerod, Dr. Thomas DeMarse, Dr. Cynthia Johnson, and Dr. Marcelo Febo for all of their support throughout this study. They have assisted me in countless ways as we worked towards the same goals of performing valuable research and helping to improve the lives of others in the world around us. Thank you to the University of Florida and the Biomedical Engineering Department for giving me this incredible opportunity to further my education. I would like to express my gratitude to the Florida Department of Health and GW Pharmaceuticals for believing in us as researchers and supporting this study.

Thank you to all of the support staff from the UF Shands Pharmacy, the UF Clinical and Translational Science Institute, UF Pediatrics, the nurses from the Clinical Research Center, as well as Victoria Evans for all of her time and efforts. Most importantly I would like to thank the participants of this study who I have had the honor to work with for the last year. Their perseverance through difficult times is nothing short of amazing and it has been a privilege to be a part of their journey and to give them an opportunity to live a better life. For that I will be eternally grateful.

And of course – Go Gators!

Disclosure of approvals and conflicts of interests

This study and all noted measures have been approved and supported by the Florida Department of Health, GW Pharmaceuticals, the United States Food and Drug Administration, and the University of Florida Institutional Review Board. The author, study team members, and support staff had no conflicts of interest to disclose.

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2-AG	2-Arachindonoylglycerol
ABC	Aberrant Behavior Checklist
AED	Anti-epileptic Drug
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
BBB	Blood Brain Barrier
CB1	Cannabinoid Type 1 Receptor
CB2	Cannabinoid Type 2 Receptor
CBC	Cannabichromene
CBD	Cannabidiol
CBDV	Cannabidivarin
CGI-I	Clinical Global Impression-Improvement Scale
CLB	Clobazam
CLN	Clonazepam
CNS	Central Nervous System
CSHQ	Children’s Sleep Habits Questionnaire
DEA	Drug Enforcement Administration
DoH	Department of Health
DZP	Diazepam
EEG	Electroencephalogram
FDA	Federal Drug Administration (U.S.)
GABA	Gamma-Aminobutyric Acid
IGE	Intractable Generalized Epilepsy
IND	Investigational New Drug

IQ	Intelligence Quotient
IRB	Institutional Review Board
NIH	National Institute of Health
QOL	Quality of Life
QOLCE	Quality of Life in Childhood Epilepsy Questionnaire
SCQ	Social Communication Questionnaire
SE	Status Epilepticus
STP	Stiripentol
THC	Delta-9-etreahydrocannabinol
TRP	Transient Receptor Potential
TSC	Tuberous Sclerosis Complex
VABS-II	Vineland Adaptive Behavior Scales II

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

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By

Christopher Logan Anderson

May 2017

Chair: Brandi K. Ormerod
Co-chair: Paul R. Carney
Major: Biomedical Engineering

As part of a nationwide physician expanded access program, the motivation of this study was to evaluate the safety and efficacy of the investigational new drug cannabidiol (CBD)(Epidiolex, GW Pharmaceuticals) in children with intractable generalized epilepsy (IGE). Thirty-three patients between the ages of 2 and 16 (average age 10.4 years) entered the study with an average of 220 seizures per month (range 7-3905). The patients (n=33) experienced four different seizure types while using varying combinations of 12 different Anti-epileptic Drugs (AED) (average 2.8 AEDs each). Before CBD treatment, and again after 6 months, patients underwent assessments to track any adaptive behavior and daily function changes that may occur. Seven patients had an IQ score above 70 and 26 scored below 70 at the start of the study. To monitor safety, blood draws, plasma levels, and vital signs were completed at each clinical visit. Patients received CBD at a dose of 25 mg/kg/day in addition to their currently used AEDs for a total of 6 months, with all seizure activity recorded in diaries. Our findings from this study were encouraging. Twenty-one of the 33 patients were considered responders, having a reduction of > 50% seizure activity. Fourteen had >80% seizure

activity reduced, with three being completely seizure free. Assessments showed improvement in disruptive behavior, social interaction, and quality of life. No safety concerns from blood tests and vital signs were found, though there was notable interaction between CBD and other AEDs, particularly clobazam and clonazepam, resulting in some reported side effects. Ten patients had one-hour EEG recordings taken before starting the study and 6 months after CBD treatment began. Readings and quantitative analysis show a statistically significant reduction in epileptiform activity and discharges. These changes in brain electrical activity correspond to seizure reduction and cognitive transformations seen by the same patients. Our study shows that CBD has a significant positive effect on seizure activity as well as quality of life in children suffering from IGE. The data presented can be utilized to better refine CBD as a treatment option and the use of quantitative EEG as a method for assessing CBD efficacy in children with epileptiform discharges.

CHAPTER 1
CURRENT MEDICAL CANNABIS RESEARCH

History of Cannabis in Medicine

Cannabis, one of the world's oldest crops to be cultivated, has been a historically significant part of mankind's way of life; from religion and agriculture, to politics and medicine, with its extensive use known to be more than 12,000 years old and continuing on to present day.[1] Throughout its journey around the world, cannabis has been commonly used in the form of one of its two main subspecies; hemp used in manufacturing practices, and marijuana, consumed for its psychoactive and medicinal properties. This naturally grown herb had humble beginnings, originating from Central and South Asia where the Mongolians found its calming effect, when smoked, to be ideal for spiritual practices and everyday recreation to create a 'zen-like' state of mind.[2] The Ancient Chinese also found hemp to be a valuable commodity, making clothing, sails, and rope with its fibers.[3] It was also here where cannabis was tried in medicinal practices, noted to work well as an anesthetic for surgeries.[4]

Eventually cannabis made the journey with nomadic tribes to the Middle East, where its anti-anxiety capabilities were highly sought after and commonly used for religious purposes, and east to Korea and Japan where its use was first known to be subjugate because of its 'socially disruptive consequences'.[5] The first documented use of cannabis for treating seizures, which is the focus of our research, occurred was around 1100 AD by Arabic writer al-Mayusi.[6] Cannabis continued its cultural migration to western lands and Africa by means of trade and invasions, where the drug persisted to intertwine itself in rituals, mercantile practices, and especially in recreational use where marijuana was experimented with in food, drink, and other amalgamations.

Roman, Germanic and other European peoples still found significant medicinal value in the plant, known to utilize it for relieving pain caused by trauma, in dentistry, and even during child-birth.[2,7] During the 15th century, the use of cannabis for controlling seizures was again noted, where historian Ibn al-Badri wrote of an epileptic child being treated with cannabis and "it cured him completely, but he became an addict who could not for a moment be without the drug".[8] It was in 1484 where the first prohibitions for cannabis were enacted when Pope Innocent VIII issued a decree claiming the plant to contain 'demonic potential'.[9]

Capitalism continued to move cannabis around the world, finding its way to Columbia, Portugal, Brazil, Chile, and the New World by European influence. Hemp became a staple in the new colonies, where the drug continued to be grown by most farmers, and even required by some townships, to be used to make paper, fishing nets, rope, clothing, and other materials. Cannabis is so entrenched in the core history of what would become the United States, that even George Washington and Thomas Jefferson would grow the plant on their own land, eventually writing the Declaration of Independence on hemp-made paper.[10] Invention of the cotton gin would soon cause the production of hemp to dramatically fall, with cotton being a better substitute for making materials.[1] Documented use of the drug as a medicine dwindled for many years, eventually making resurgence in the 19th century when doctors administered cannabis for patients with epilepsy, including Queen Victoria's personal physician who claimed that, "attacks or violent convulsions…may be stopped with a full dose of hemp".[2] It was in the 1830s when the notorious physician William Brooke O'Shaughnessy performed experiments with cannabis and found that it did not have any negative medicinal effects,

a major breakthrough that helped to dispel some of the damaging beliefs that detracted from some of the benefits the drug could have. Still, cannabis continued to be known more for its non-medicinal uses and it became closely associated with alcohol, debt, and poverty when many slaves and plantation workers had continued its recreational use.[11] This was the beginning of a true political shift of cannabis use as an undesirable action, where social class and racism caused mass disapproval.

With the evidence of medical benefits slipping away from the interest of society, cannabis eventually found itself in the middle of the prohibition movements of the 1920s in America and the United Kingdom, which included alcohol and other drugs, and where the possession, raising, and consumption of the plant became illegal. Laws in the United States suffocated cannabis use for any reason including hemp, which many cotton plantation owners, who carried a lot of political influence in the young country, wanted to see die out to prevent any type of competition.[13] The down spiral continued, and propaganda against the drug was in full force, painting it as a dangerous narcotic that could destroy lives and lead to criminal activity. In 1937 the Marijuana Tax Act was passed by Congress, which gave the Drug Enforcement Agency complete control to regulate the drug, essentially criminalizing possession of marijuana across the country.[14] Little changed over the next several decades and even though hemp made strides to be and marijuana made resurgence in recreational use in the 1960's, sparking some movement towards its potential uses, strong political limitations and conservative views kept any advancement in the medical field nearly non-existent.

Today, marijuana sits next to LSD and heroin as a Schedule I controlled substance, which would indicate that there is no evidence for acceptable medical or

safe use. Though heavily restricted and fighting an uphill battle against history, the Department of Health and Human Services estimates that more than 6% of the United States population still uses the drug (Department of Health and Human Services 2008). The 21st century has brought with it another wave of progress and views, as a liberal youth movement has led to a majority of people in the United States to support the legalization of marijuana. In 2012 Colorado and Washington legalized the drug for recreational use, a bold step forward as the first states to regulate and tax its private use. The impact was almost immediate, with Colorado reporting nearly $40 million in tax revenue and a decrease in both violent crime rates and unemployment in the years to follow.[14]

Much of the research looking at marijuana as a treatment option is quite limited, and most knowledge comes from anecdotal reports or preclinical studies on animals.[15] There are, however, several reports available on a number of case studies and surveys performed over the last few decades showing that cannabis, in various forms, has an anticonvulsant effect on individuals with epilepsy and seizure activity with fewer and less severe side effects than other FDA approved medications.[16] Many physicians specializing in epilepsy or neurology in the United States are becoming aware of these new studies and are beginning to acknowledge the potential benefits the drug possesses, looking for more human clinical trials to be performed to draw more concise conclusions. It is now, as patients are seeking better treatment options, that medical marijuana has been becoming increasingly popular on political and medicinal agendas, with 23 states taking actions to legalize its use for various diseases and ailments and both the American Medical Association and American College of Physicians are calling

for more research to be done as well.[17] Looking at the long and complicated history of cannabis, it is easy to see how a drug with evidence of strong medical potential was lost in a world controlled by religious and political ideologies. Centuries of various uses and negative connotations have often swayed public opinion and buried the signs of medicinal possibilities, limiting what could be valuable to those who are in desperate need of better treatment options and quality of life. With a new era of compassionate medicine beginning and a strong movement for legalization brought on by public opinion and a more open-minded perspective, cannabis will be getting the attention it desperately needs and deserves from scientists and researchers alike.

The Evidence of Cannabis for Childhood Epilepsy and Seizures

As noted, economic and political interests in the United States have largely made research scarce and finding detailed information on the efficacy of the drug as a medicine a difficult undertaking. While much of this research is anecdotal, there have been a few recently published case studies, surveys, and small trials looking at the effects that cannabis has on seizure activity and epilepsy in children. An unreported number of families have turned to alternative forms of treatment in an attempt to wrest control of their children's health from ineffective antiepileptic drugs (AEDs), with the most common of these home remedies being cannabis.[18] Although still restricted in several states, many families willingly risk the consequences based on the anecdotal evidence of success.

Cannabis, as a plant, is made of nearly 483 known compounds called cannabinoids.[16] The two most commonly studied, and the focus of epilepsy research, are tetreahydrocannabinol (THC) and cannabidiol (CBD). THC is well known as the major psychoactive ingredient and CBD is the key nonpsychoactive component in

cannabis. In August 2013, CBD gained headway to becoming a household name when a CNN news article told its readers of the journey of a young six-year-old girl named Charlotte Figi, who was diagnosed with Dravet Syndrome, a rare form of epilepsy.[19] By the age of three, Charlotte was having an average of 300 grand mal seizures (the most severe seizure type) per week and her condition was worsening to the point that physicians were suggesting a medically induced coma to give her battered body a rest. Numerous failed treatment attempts and the reality that there was nothing the hospital could any longer do, Charlotte's parents decided to try a specific strain of marijuana for their daughter after reading of a child in California who had been successfully treated with cannabis.

After a long trek through the legal system, and the agreement of two medical practitioners, Charlotte received marijuana that was noted to be low in THC and high in CBD. The results were immediate, making Charlotte seizure free after a week of use. With such an astounding outcome, but a low supply of drug, the Figi family was put in touch with the Stanley brothers, a group of marijuana growers in Colorado who had grown a strain that was low in THC and high in CBD, which had proven to be difficult to sell. The pairing was meant to be, as the brothers began to market their new strain of marijuana, now known famously as 'Charlotte's Web', to be used as a potential viable option for others in similar situations. Immediately the larger scientific community started discussing clinical implications of using CBD to treat epilepsy and pharmaceutical companies began their own drug development and testing. CBD, shown to have non-psychoactive properties, became the main source of interest in medicine, for children in particular, due to fewer resulting side effects. While this remarkable story gave medical

marijuana the push it desperately needed, clinical studies and evaluations are required to better understand the efficacy of the drug, as well as its safety, as the medical and pharmaceutical researchers contend with current preconceived misconceptions about the unethical use of medicinal marijuana. Significant examination of CBD for human use rapidly began, leading to more critical and sophisticated surveys and studies. Table 1-1 highlights the most recently reported clinical evidence of CBD being used to treat epilepsy for durations greater than three months.

Table 1-1. Reported clinical evidence of CBD for childhood epilepsy.

Study (Year)	Study Type	Total Subjects	Epilepsy Type	Duration (median months)	CBD Dose (median mg/kg/day)	Results
Devinsky (2016)	Open Label EAP	137	Mixed Refractory	3	25	Median monthly seizure frequency was -36.5% from baseline. Five children were seizure free.
Cunha (1980)	Randomized Parallel Double-blind Placebo trial	15	Uncontrolled	4.5	200 - 300	4 had 100% reduction, 3 >50% reduction, and 1 no change
Hussain (2015)	Survey	117 Parents	Epilepsy	6.8	4.3	85% had reduction in seizures and 14% were seizure free
Porter (2013)	Survey	19 Parents	Mixed Refractory	4	0.5 – 28.6	2 had 100% reduction, 8 had >80%, 3 had >50%, 3 had >25%, and 2 had no change
Devinsky (2014)	Open Label EAP	29	Mixed Refractory	3	25	14% had 100% reduction and 39% had >50% reduction

Double-blinded studies using CBD and a placebo control for epilepsy treatment are few and only one has been published to date. Of those that data was available from, the low number of subjects involved makes it difficult to provide consistent and sufficient data to prove effectiveness of the drug. While the obvious conclusion to remedy the

ineffectiveness of these smaller studies would be to perform them with a larger patient population and a more long-term treatment plan to better assess safety and efficacy, they do give us a snapshot of the possible placebo effect that many federal agencies claim could be a possible explanation for ‘claimed success’ with CBD treatment. These initial studies begin to assess the tolerability and most importantly the safety of cannabis as a medical treatment option.

One of the smaller studies included fifteen patients with generalized epilepsy who were randomly divided into two groups, all of whom received a double-blinded 200 to 300 mg/kg daily dosage of CBD or placebo along with their current AEDs.[20] Of the 8 who ended up receiving CBD, 4 were seizure free, 3 had greater than 50% reduction of seizures, and one had no change in seizure activity. Only one of the seven patients in the placebo group noted an improvement in seizure frequency at the end of the trial. While low in sample size, studies such as this show the importance of using double-blinded and placebo controlled studies for CBD research.

In another study, an online survey was completed by parents who had administered high-CBD preparations for their children with epilepsy, most of whom were specifically diagnosed with Lennox-Gastaut, a particular form of epilepsy in which there is similar uncontrolled seizure activity, where the location of seizure origination in the brain can often be detected by EEG. Nearly 85% of all parents reported that the CBD treatment caused a reduction in their child’s seizure frequency, with 14% claiming they were seizure free. Parents also noted an improvement in daily mood and sleep after taking the drug.[18] A similar, more thorough, survey was performed at Stanford University, where 19 parents were asked about the effect or lack of effect of CBD on

their children's seizure frequency.[21] The children ranged in age from 2 to 16 years. Thirteen children had Dravet syndrome (one of whom had epilepsy in female with mental retardation, EMFR), three children had Doose syndrome, and one each had myoclonic astatic epilepsy, Lennox-Gastaut syndrome and idiopathic early-onset epilepsy. The children experienced a variety of seizure types including focal, tonic-clonic, myoclonic, atonic and infantile spasms. The children had unsuccessfully tried an average of 12 other AEDs before their parents began CBD-enriched cannabis treatment. The doses of CBD the parents reported providing ranged from less than 0.5 mg/kg/day to 28.6 mg/kg/day. The doses of THC contained within those samples were reported to range from 0 to 0.8mg/kg/day. To obtain dosage information, parents had their preparations tested at commercial medical cannabis testing facilities. Seizure frequency before administering CBD-enriched cannabis ranged from 2 per week to 250 per day. To validate the survey, the researchers used the same survey with a comparable group of parents, inquiring about the effects of an AED approved in Europe for Dravet Syndrome, stiripentol (STP).

Sixteen (84%) of the 19 parents participating in the survey reported a reduction in their child's seizure frequency. Two parents reported that their child became seizure-free after more than 4 months of CBD-enriched cannabis use. Of the remaining 14 parents reporting a change in seizure frequency, 8 reported a greater than 80% reduction in seizure frequency, three reported a greater than 50% seizure frequency reduction and three reported a greater than 25% seizure frequency reduction. Three parents reported no change. Twelve parents weaned their child from another AED after starting CBD-enriched cannabis treatment. Beneficial effects of CBD-enriched cannabis

reported by the parents, other than reduced seizures, included better mood (15/19, 79%), increased alertness (14/19, 74%), better sleep (13/19, 68%), and decreased self-stimulation (6/19, 32%). Negative side effects included drowsiness (7/19, 37%) and fatigue (3/19, 16%).

Limitations of the data from this study include lack of control data, lack of randomization and blinding associated with open-label use, as well as uncertainty of the dosage in artisanal preparations. The wide age range is something to note as well, as it is not well established what effect CBD may have on the highly plastic brain of a 2-year old compared to one that is more developed at the age of 16-years. That said this is also the ideal age target for epilepsy patients as any seizure control can assist with future development into adulthood. It should be noted there is also inherent error in parent reporting and validity of qualitative data. However, this survey lends hope that CBD may be a useful pharmaceutical alternative to existing therapies in drug resistant epilepsy, and sheds light as to what doses are being used experimentally by parents that appear to be well tolerated. The authors of the study note the need for future research to assess any long-term behavior or cognitive changes that may occur after extensive use of the CBD by children, though they assume the risk outweighs any current deficits.

A more recent study performed by Devinsky et al.,[22] employed an expanded access program to determine the efficacy and safety of Cannabidiol (Epidiolex, GW Pharmaceuticals) in children and young adults with treatment-resistant epilepsy. Twenty-three patients, ranging from ages 3 to 26 (median age of 10.4 years) entered the study with 9 diagnosed with Dravet Syndrome, 4 had Myoclonic-Absence Epilepsy,

3 Lennox Gastaut, and the others with generalized epilepsies. All patients underwent a 4-week baseline period where parents and caregivers recorded all seizures and seizure type in a study-provided diary. After baseline data was determined, the patients were then given a purified oil-based extract with a known composition of 98% CBD at a dose of 5 mg/kg/day in addition to their currently used AED's. Their daily dose was increased by 5 mg/kg/day until a maximum dosage of 25 mg/kg/day was reached. Patients received the CBD treatment for a total of 3 months with seizure data continued to be recorded in provided diaries.

All patients enrolled completed the 3 months on the study drug, with nine (39%) of the 23 patients having a greater than 50% reduction in seizures, and a 32% median reduction in seizures across all patients. Four (17%) of the patients were seizure free at the end of the 3 months, with three of the four notably having Dravet Syndrome. It was also noted that of those who entered the study with Dravet Syndrome, 44% (4/9) had a greater than 50% reduction in seizures and 33% and a 40% median reduction from baseline, overall. Some notable side effects were also reported, including somnolence (57%), fatigue (57%), decreased appetite (22%), diarrhea (22%), and weight loss (9%). Due to the severity of some of these side effects, the dose of CBD was reduced from 25 to 20 mg/kg/day, which resulted in improvement of these symptoms. It was also significant that five patients had their clobazam dosage reduced due to its potential interaction with the CBD possibly causing heavy sedation.

Here the benefit of a clinically run trial compared to that of survey collected data is evident with more directly reported data under known and controlled dosages of CBD. It can also be noted that CBD has a significant effect on seizure activity in the

adolescent population. Considering the variety of epilepsy disorders and limited controls, this study raises many more questions in regards to what types of neurological disorders may have an impact on CBD efficacy (shown by a higher response in Dravet Syndrome patients) and what other neurological and behavioral benefits or changes other than reduced seizures could result from use of the drug. In a second study, the same research group compiled the results from eleven different epilepsy centers across the United States, using the same protocol and CBD-based drug, Epidiolex.[23] The primary outcome measure was to review safety and tolerability, with a secondary measure of monthly seizure frequency changes. The target group was, again, children and young adults suffering from treatment-resistant epilepsy, with 162 patients evaluated for safety and adverse events, and 137 (from the same group) were included in the efficacy analysis for seizure frequency reduction. Thirty-three of those 137 patients had Dravet Syndrome, 31 had Lennox-Gastaut, and the remaining 73 had varying intractable epilepsy diagnoses. During the study, a number of adverse events were reported, and those with >10% of occurrence in patients included somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsion (11%). Serious events were reported by 30% of the patients during the 12-week trial, with 20% possibly being related to CBD use. It was noted that the titration period for the study drug was slow with a lot of variability between patients, with most subjects not at a stable dosage until more than halfway through the trial. It was for this reason that the study group determined to only analyze the last 4-weeks of seizure activity compared to baseline. Out of all patients, 54 (39%) had >50% reduction in seizure frequency, 29 (21%) had >70% reduction, and 9 (7%) were completely seizure free. The research

group noted that the number of serious adverse events reported was much higher than expected, but with no control group and a high number of other antiepileptic drugs used by the patients (an average of 3 each), it was difficult to accurately determine if the CBD contributed to these events. They also believe that, while the evidence presented shows CBD to be highly effective for seizure frequency reduction, safety and efficacy needs to be assessed in controlled studies using consistent study medication for specific epilepsy syndromes.

Researchers recently published evidence of CBD use as a treatment of refractory epilepsy in tuberous sclerosis complex (TSC).[24] Using the same drug, Epidiolex, ten pediatric patients with a definite diagnosis of TSC and refractory epilepsy were treated for 12 months. The safety, efficacy, and changes in behavior and cognition were assessed throughout the study. The results showed an improvement in response rate over time from 50% to 66% of the patients having >50% reduction in seizures after the trial had ended. Parents reported improvements of alertness, verbal communication, cognitive ability, and expression of emotion. It was detailed that more than half of the participants experienced side effects, but most or all were relieved after their other AEDs or current CBD dose was adjusted. While this study includes a very small sample size, it does suggest that CBD is safe and can be an effective treatment option for children with refractory epilepsy and TSC.

It is also important to note that no current studies report the long-term efficacy and safety of CBD, nor if CBD alters the comorbidities associated with chronic seizures. Most of the studies detailed do assess the immediate impact on the individuals being administered CBD and have found the compound to be both safe and with minimal side

effects, but they do not reach beyond the short-term study use. Examining the safety of using the drug over time will be necessary, especially when considering its effect on the developing brain of a child. As research continues and the use of THC in conjunction with CBD for medicinal purposes expands, it will be even more crucial to assess the safety of these cannabinoids. While CBD is sought after for its lack of psychoactive effects, the benefits of THC cannot be ignored. Neither CBD nor THC has ever had any reported deaths associated with overdoses, though related accidents to a high intake have been noted by a number of news sources, noting that paranoia, hallucinations, and withdrawal could be of concern without proper intake monitoring. With an increase in emergency room visits in Colorado,[26] which have been correlated to the state-wide legalization of marijuana for recreation and medicinal use, proper research needs to be conducted to either alleviate or caution its use before physicians can appropriately recommend its use to their patients.

The studies demonstrated the benefits of a clinically conducted, case-controlled trial compared to that of survey or observational collected data, with more directly reported data under known and controlled dosages of CBD. We also see that CBD has a significant effect on seizure activity in this young population. With varying epilepsy disorders and limited controls, this study raises many more questions in regards to what types of neurological disorders may have an effect on CBD efficacy, shown by the higher response in Dravet Syndrome patients. GW Pharmaceuticals, the producers of Epidiolex, have openly reported success of their CBD-based drug in children with Dravet syndrome and Lennox Gastaut (ClinicalTrials.gov: NCT02224703 and NCT02224560). Moving forward they have begun double-blinded trials for the same

patient populations to address the FDA's concern over placebo controls as well as smaller studies looking at other epilepsies, including the aforementioned TSC trial, as examining the efficacy in children with refractory epilepsy.

These results also suggest that use of CBD may be linked to other neurological and behavioral benefits or changes, other than seizure reduction. Scientific evidence and clinical testing is beginning to support the use of cannabidiol as a medicinal therapy, and with it come many more questions about the drug and how it can be studied and used more effectively in medicine. While parent reported results can be a valuable measure of efficacy and changes in child behavior, they are susceptible to the reporting bias with many wanting to see a desired effect, making more standard clinical measures of cognition and behavior important in future studies. Performing trials using CBD with a cohort of participants with similar deficits and diseases, as well as control over AED use, will help us better understand the influence of these variables. Simple, yet straightforward studies would assist in demonstrating the causality of the CBD's effects, determining how truly significant this new area of medicine can be while insuring that the use of other AED's and treatments are not intervening with the recorded outcomes.

Difficulty of Performing CBD Research

While cannabis, and namely CBD, is becoming an increasingly popular topic of both political agendas and for research, it is still challenging to find clinical trials being performed. The main reason for the lack of testing is again tied to the restrictive and legal circumstances surrounding the drug, making it extremely difficult to get any study approved by protective research agencies or even funded due to the inherent unknowns. With marijuana still listed by the Federal Government as a Schedule I

substance, hurdles are immediately placed in front of researchers interested in studying the drug in its various forms. To perform any clinical research with marijuana, one first needs a DEA license, which allows the drug to be legally prescribed as an investigational new drug (IND). A DEA license can only be acquired by an experienced physician practicing in the state where the research is allowed. Application for the license is commonly a three to four month process that scrutinizes the applicant's personal proficiencies and records as a clinician. The study then needs to be approved by the Federal Drug Administration (FDA), the National Institute of Health (NIH), and the Research-State's Department of Health (DoH), all of which require significant financial backing and the time to complete registrations in order to prove the value of the proposed research.

After the licensing, approval, and financial milestones have been reached, the proposed study must meet all standards set forth by the Institutional Review Board (IRB), whose focus is to review, approve, and monitor any biomedical research that is to be performed on human subjects. With very little scientific evidence of CBD use in humans, especially with children, providing enough proof to assist in the risk-benefit analysis of the requested research is extremely difficult. It is also difficult to prove how the welfare of the subjects who would be participating can best be protected. Many researchers still face the bias and stigma that is prevalent in the legal community and in society in regards to cannabis and its use. Once all reviews are completed and the aforementioned governing bodies give their approval for the study, the process of acquiring the necessary staff, clinical tools and space, study drug, participants who meet the study criteria, and maintenance of appropriate protocols begins. Overall, the

entire process of getting a study involving medical marijuana approved, if it is well supported and all of the avenues needing be taken are not blocked, can take well over a year or more to complete.

The study design and approval experience for our research group faced all of the same challenges previously described during the conception and design of the protocol that this doctoral dissertation focuses on. The main goal of our study was to provide treatment with CBD to children with drug resistant epilepsy through a Physician Expanded Access Investigation New Drug protocol designed by our study team. The greatest assistance came from both GW Pharmaceuticals, who provided the high-CBD drug (brand name Epidiolex) that had been approved by the FDA for investigational use, and the Florida Department of Health, who funded the study. Dr. Paul Carney, a neurologist licensed in Florida with decades of experience in epilepsy research, acquired approval for an Intermediate Size Patient IND under the expanded access program. The approval allowed us to provide treatment with Epidiolex to 50 patients with drug resistant epilepsy. The study patients had exhausted the majority, or in some cases, nearly all viable FDA approved treatment options. Once FDA and NIH requirements were met and support given by the Florida DoH, it was then determined by the University of Florida's IRB that the potential benefit of improved seizure control outweighed any risk of treatment with this investigational product since the safety profile provided by our study team appeared to be favorable.

Upon approvals being given to move forward with providing the 50 participants with the CBD to treat their epilepsy and seizure activity, the process of recruitment began. Thirty-five participants, who are the focus research cohort of this dissertation,

were accepted into the study at the University of Florida and fifteen others at the Miami Children's Hospital in Miami, Florida. A complete analysis and review of this study is detailed in the remaining chapters of this dissertation. Like many other studies, this drug protocol required constant upkeep and regulatory control in order to insure that such high profile research was being completed in both the safest and most legal manner with the participant's well being always being the top priority. Research such as our study is often the victim of politics surrounding marijuana and its related compounds, with circular logic preventing groups like our own to make advancements in better understanding the safety and efficacy of this potential treatment. While the mentioned agencies are required and warranted in order to protect human participants and their family members, as long as marijuana remains a Schedule I drug, other studies that look to follow will continue to face the same obstacles preventing progress. After a long road filled with many renditions and attempts, we were fortunate enough to complete our study and will hopefully help to move medical marijuana and CBD research forward so that it can be better studied and available for those in need of better options.

CHAPTER 2
INTRACTABLE GENERALIZED EPILEPSY AND CANNABIDIOL

Understanding Intractable Generalized Epilepsy

Antiepileptic drugs (AEDs) are the leading treatment option for symptomatic management of seizures for patients with epilepsy. Pharmacological treatment of epileptic seizure activity has been widely used since the early 1900's with the development of drugs such as phenobarbital, phenytoin, carbamazepine, and valproic acid, all of which are still currently being prescribed by neurologists.[27] A number of other AEDs have been released in the last 20 years with varying pharmacokinetics and side effects.[28] AEDs are not an effective treatment option for all epilepsy diagnosis, however. It is estimated that nearly one third of all patients with epilepsy are likely to not respond to AED therapies.[29] When these patients fail to have control of their seizures after an adequate dosage of at least two AEDs, they are categorized as having Intractable Epilepsy, also known as 'drug-resistant' or 'refractory' epilepsy. This severe form of epilepsy has a common onset in early childhood and an incidence of around 1 in 40–50,000,[30,31] accounting for 4.3% of all childhood epilepsies.[32]

There are several reasons that seizures are unable to be controlled in this cohort of children. The most common reasons are believed to be the result of an incorrect diagnosis, insufficient control of lifestyle factors, genetic underlying conditions, development of medication tolerance (resistance), harmful side effects from AEDs, or even inappropriate AED choices.[33] Some scientists believe that transport pumps in the blood brain barrier (BBB) could be in excess in patients with intractable epilepsy.[34] Cells in the BBB allow for transcellular crossing of nutrients and other compounds to the brain while keeping out harmful or unidentified toxins. AEDs rely on assistance from these

cells to enter the brain as well as to maintain specific levels of prevent drug concentrations from becoming overwhelming. Sodium and chloride conductance play a significant role in the control and maintenance of seizure discharges and neuronal transmissions. While the exact mechanisms of most AEDs are not known, it is expected that they either block sodium channels to prevent rapid repetitive neuronal discharges or alter the frequency that chloride channels open to elevate seizure threshold. An excess of transportation pumps could both prevent AEDs from entering the brain to make necessary modifications as well as keep dosage levels below what can be effective. The challenge with finding a suitable AED for the correct seizure type is that when at least two AEDs fail to bring seizure activity under control, there is only a 5-10% likelihood that a third or more drugs will be effective,[35,36] with this statistic even being considered as a notable indicator for predicting intractable epilepsy.[37]

Physicians would prefer to prescribe children with the fewest AEDs for seizure control as possible, ideally with just a single drug as monotherapy has shown to have few or no drug interactions with any other non-AEDs the patient may be receiving.[38] With most AEDs having little to no effect on seizures, or the correct drug not determined, it is difficult and often impossible for these patients to be suitably treated with a single drug. As a result many physicians enact a combination drug therapy using a number of AEDs all at once to attempt some form of seizure control. Unfortunately, there is a proportional relationship to the number of drugs a patient is taking and the severity of side effects. For this reason, the interactions of AEDs and other drugs can create many problems that can only worsen the wellbeing of the patient. Use of several

AEDs can negatively impact epilepsy related co-morbidities such as anxiety, mood, and cognition.[39]

With AEDs having little to no impact, or having intolerable adverse effects, surgery often becomes the only reasonable option for some children. Physicians and surgeons look for a focal point in the brain where the seizures originate. This requires the location of the seizure onset to consistently be from the same area of the brain and in an area that can be safely altered or removed without creating any cognitive damage or disability. If the child fits the criteria, surgery is often recommended. Multiple studies show that there is approximately a 40 to 50 percent chance of being seizure free for life, with improved cognitive and memory function compared to those who do not undergo surgery.[40] There are exceptions for a patient not being a suitable candidate for epilepsy surgery, with the most common being those who have seizures that appear to originate from multiple areas of the brain simultaneously with no specific onset. This condition occurs often in children and is designated as generalized epilepsy, which includes absence (highest occurring), myoclonic, tonic-clonic (also known as grand mal), and atonic (drop attack) type seizures.

Intractability and generalized seizure activity are often diagnosed together. Children living with these conditions that do not benefit from FDA approved AEDs are not suitable surgery candidates, and they suffer with a number of physical and cognitive deficits as a result. Those deficits may include cognitive decline, comorbidity,[41] psychological deficits,[42] reduced quality of life, and high mortality rates.[43] Among children with intractable epilepsy, those suffering from early-onset and high seizure burden epilepsies suffer the greatest neurodevelopmental problems. Due to the broad

spectrum of behavioral symptoms in this population, it is often challenging to identify effective treatments. An optimal medication would improve social interactions and reduce seizure frequency without significant motor, emotional, and cognitive side effects. Recent evidence suggests that more effective early control of epilepsy is associated with better developmental outcomes compared to patients who had less treatment options 20-30 years prior.[39] It is obvious that these children need a more effective medical therapy to improve quality of life and alleviate neurodevelopment deficits. An ideal treatment would reduce the severity and frequency of epileptic activity, eliminate the reliance and use of concomitant drugs, have limited side effects, and lead to improved behavioral and cognitive function.

Pharmacology of Cannabidiol and Potential Role in Epilepsy

Cannabis has demonstrated its potential for the therapeutic treatment of a variety of ailments and diseases. The naturally grown plant contains over 80 different biochemical compounds called cannabinoids, many of which share very similar chemical structures and active properties.[44] Cannabinoids are often classified into three sub-groups: Phytocannabinoids, endocannabinoids, and synthetic cannabinoids. Phytocannabinoids are the cannabinoids that are found naturally in the cannabis plant, of which THC and CBD are the most prevalent. Endocannabinoids are chemical compounds found throughout the body including the heart and immune system, and predominantly in the central and peripheral nervous systems, which activate receptors for cannabinoids and act as neuromodulators for a number of neurological processes. Allyn Howlett and William Devane first discovered and characterized the receptors specific to endocannabinoids in a rat brain in 1988.[45] It was found that these receptors were some of the most prevalent in the brain and are far more abundant than any other

neurotransmitter receptor, making them a critical component to neurological processes. 2-Arachindonoylglycerol (2-AG) and anandamide are two of the most abundant endocannabinoids in the body and have been shown to regulate immune system functions as well as sensory receptors associated with pain and hunger.[46] Synthetic cannabinoids are man-made compounds that are vastly different from their natural counterparts, but claim to possess similar psychoactive and medicinal effects of cannabis. Recent analyses of these synthetic products have found them to be much less effective and have a higher risk of adverse effects including psychotic episodes and seizures.[47] It is for this reason that medical research is turning away from synthetic cannabinoids and focusing on phytocannabinoids and the effect they may be having within the endocannabinoid system. As noted, two most commonly noted and studied cannabinoids are delta-9-tetrahydrocannabinol (THC), known for its psychoactive qualities that create an effect many describe as being 'high', and Cannabidiol (CBD), which is the motivating cannabinoid being focused on in this dissertation and is non-psychotropic, often making it the ideal focus for medicinal research.[48] The numerous other cannabinoids found in the plant are less in ratio and understudied compared to THC and CBD, though potential medicinal qualities have been shown in some experiments where cannabidivarin (CBDV) and cannabichromene (CBC) may be used as anti-inflammatories or anticonvulsants.[49,50]

In recent years, as legal restrictions have lessened their grip, cannabis growers have been able to develop refined breeding practices for producing plants with both high THC and CBD content.[51] This horticulture process is not perfect, however, and with various preferences in techniques and growing capacities of many nurseries, there is

often variability amongst plant content, resulting in inconsistent medicinal products for patients without the pharmaceutical quality control and refinement that other AEDs are subjected to. The unreliability in the consistency of plant content is another hurdle making medical research with THC and CBD difficult. There are a number of strains and products available to patients with varying cannabinoid content, so that consistent measures of efficacy are challenging to quantify. For this reason, the use of one particular strain of medical marijuana with a focused cannabinoid and established chemical makeup in any study is very important in order to draw concise conclusions.

The precise mechanisms of action of cannabinoids are not completely understood, though studies have isolated and characterized both THC and CBD to better recognize their pharmacology. Recent progress in understanding the endogenous cannabinoid system has allowed new insights into the effects of cannabinoids in their anti-convulsive activities. The endocannabinoid system is a very complex physiological system where cannabinoid receptors are found to interact with these natural chemicals. When excessive neuronal activity occurs, endocannabinoids are generated on demand and activate G-protein-coupled receptors, known as cannabinoid type 1 (CB1) and type 2 (CB2) receptors.[52] CB1 receptors are most prevalently found in the presynaptic axon terminal, and regulate both GABA and excitatory glutamate release from the inhibitory regions.[53] Control of GABA and glutamate is significant as both play an important role in inhibiting or exciting neurotransmission within the central nervous system as well as a significant number of synapses throughout the entire brain.[34] In a model of epileptiform seizures, it has been shown that CB1 receptors expressed on excitatory glutamatergic neurons modulates effects in the central nervous system (CNS)[52] and in turn mediates

the anti-convulsive activity of endocannabinoids.[54] CB2 receptors are more commonly found in immune and neoplastic cells and it is expected that they also play a role in neural modulation.[53,55] These qualities make the endocannabinoid system and its receptors very important for controlling the rapid firing of neurons that overwhelm the brain and cause seizures or epileptic discharges. It is believed that cannabinoids introduced into the system work to stabilize the central nervous system by inhibiting neurotransmitters, such as glutamate, and reducing any abnormally high neuronal activity.

THC has been found to bind to both the CB1 and CB2 receptors and act as an agonist.[45] When excessive neuronal activity occurs, endocannabinoids are generated on demand and activate CB1 receptors. The systemic activation of CB1 receptors by exogenous cannabinoids, such as THC, generally reduces the release of neurotransmitters and in turn reduces or controls activity. However, the application of CB1 agonists does not always target the appropriate neuronal subpopulation containing CB1 receptors and induce a protective effect.[54] In fact, the opposite may happen, and the treatment could potentially worsen the seizure frequency. This is where CBD, which is understood to be an antagonist for CB1 and CB2 receptors, can be beneficial. Unlike THC, CBD only weakly binds to CB1 and CB2 receptors and establishes antiepileptic contrivances likely outside of the endocannabinoid system.[56] While the exact mechanisms of CBD are not well understood, it is believed that this cannabinoid prevents neuronal hyperexcitability by modulating activity of the neurons via its pharmacological profile.[57] CBD does inhibit the CYP2C19 metabolic receptors, which

are used by several other antiepileptic drugs to enter the central nervous system and neuronal pathways.[58]

Some studies have linked CBD to increased inhibition of GABA receptors and regulation of calcium channels, which could also result in an anticonvulsant effect.[45,59] Underlying neural mechanisms of epilepsy are often related to increased glutamate/GABA activity, which sometimes results in excitotoxicity, or over activity, that can cause eccentric neuronal connectivity with resulting seizure and behavior deficit.[60] CBD controlling glutamate or GABA activity results in decreased epileptic activity as well as having a corresponding change in cognition or behavior. Likely it is the stacking of all of the effects from CBD that helps to modulate neuronal activity and reduce epileptic discharge. Other noted mechanisms of action of CBD that include antagonizing G-protein-coupled receptors by binding to members of the TRP cation channels at low levels, leading to decreased presynaptic release of glutamate[61,62] inhibiting adenosine reuptake,[63] and activating 5-hydroxytryptophan 1A receptors.[64] CBD has also been noted to have both antioxidant and anti-inflammatory effects,[65] leading researchers to believe that it is likely the stacking of all of these effects from CBD that helps to modulate neuronal activity and reduce epileptic discharge.

Introducing CBD as a treatment for seizure activity and for patients suffering from intractable generalized epilepsy, where other AEDs are underperforming, could prove to be beneficial, especially for children whose brains are still developing and highly effected by abnormal activity. Recording changes in seizure activity is only one method for quantifying CBD's effectiveness as an antiepileptic treatment option, with behavioral changes and measures of quality of life also being significant to better understand how

beneficial this drug can truly be. It is here, as we look to better utilize these pharmacological properties of cannabis, that we focus on first studying the safety and efficacy of CBD for children with intractable generalized epilepsy. By performing the initial studies we can start assessing CBD as a treatment option compared to other AEDs, and with it begin asking more specific questions on how to make the drug more effective for those patients desperately in need of a viable treatment.

Study Design

The main goal of this study is to provide open label treatment with CBD to children with intractable generalized epilepsy through a Physician Expanded Access Investigation New Drug protocol using a pharmaceutically designed drug called Epidiolex (GW Pharmaceuticals, London, UK). As the controlled therapeutic use of CBD in children is novel, the primary objective of this study is to evaluate the safety of CBD when administered as adjunctive therapy in children that have exhausted a majority of FDA-approved antiepileptic drug treatment options. While recording seizure activity is a critical measurement for assessing efficacy, what makes this study unique is that it is one of the first to both examine the effects of CBD on this specific population of children with intractable generalized epilepsy as well as quantify and correlate the behavioral and quality of life alterations that are likely to result from the antiepileptic changes.

Thirty-three (33) children between the ages of two and sixteen were recruited to be a part of this study at the University of Florida. By the end of the 6-month trial period included in this study summary, three (3) participants had been removed from the study due to the study results not meeting the expectations of the parents or guardians, unrelated to any health or safety concerns. In order to be entered into the study, patients needed to fall within the age requirement, have a minimum of four clinically

countable seizures per month, generalized seizure activity, have a history of use of at least four antiepileptic drugs without beneficial seizure control, and stable doses of AEDs at least one month prior to enrollment. Patients were excluded from the study if they did not meet the minimum inclusion criteria, had used CBD or similar products less than a month before the study began, were allergic to CBD, or had any other diagnosed forms of epilepsy such as Dravet syndrome or Lennox Gastaut. Children were recruited from the Shands clinical population, State-wide Florida epilepsy collaborators, referring physicians, and/or advertisement on clinicaltrials.gov. Patients were enrolled on a first come first serve basis, as part of the agreement for expanded access use of the drug. Of the thirty-three children entered into this study, the average age was 10.4 years, 12 different AED's were used among them for an average of 2.8 each, with 17 of the children being identified as male and 16 female.

Upon meeting all inclusion and exclusion criteria, every participant, parent, or caregiver signed informed consents agreeing to be entered into the study and adhering to all requested visits and testing, as approved by the University of Florida's Investigational Review Board. Each patient was then provided with a seizure diary, where the parents or caregivers were instructed to record the number and type of seizures their child experienced over the course of the next month. Types of seizures included tonic-clonic, myoclonic, atonic, and absence seizures with notable motor features. After this baseline seizure information was logged, patients returned to the study site where they received their first dosage of Epidiolex. Epidiolex is a 98% pure oil-based cannabidiol extract of constant composition that is administered in a 100 mg per mL sesame oil-based solution. The CBD oil was first given orally or via gastric tube

at a dose of 5 mg/kg per day divided in twice-daily dosing. The dosage was then up titrated by 5 mg/kg once a week until an effective dosage was reached or a maximum dose of 25/mg per day. It was instructed that CBD was to be taken along with their current antiepileptic. All medications that were being taken by the participants in the study continued to be received at steady state dosages for the first month before CBD was introduced and continued for the first three months of treatment.

Plasma levels were taken at each study visit to maintain constant levels of AEDs with dosages being adjusted as needed to continue consistent therapy or as a result of any adverse events. After 3 months of CBD treatment the participants were given the opportunity to work with their personal neurologist or epileptologist to reduce or remove any of their other AEDs. Participants made clinical visits 1, 2, 3, and 6 months after beginning CBD treatment. All seizures continued to be recorded by the patients or their caregivers and reviewed by the study team at each visit. To monitor safety and tolerability, all adverse events and effects were monitored and recorded as well as the number of times rescue medications were used. Vital signs were measured and laboratory tests were performed for hematology and concentrations of antiepileptic drugs at baseline and every clinical visit to follow throughout the CBD treatment.

While the primary endpoint of the study was to determine the efficacy of cannabidiol on seizure frequency and its safety and tolerability with children, the other significant outcome measure was the effect of CBD on behavior and function as it relates to the child's quality of life in a corresponding relationship to seizure control. To quantify changes in behavior, function, and quality of life throughout the study, several questionnaires were administered to the parents and caregivers. An IQ test was

performed at baseline, then at every clinical visit the Clinical Global Impression-Improvement scale (CGI-I) was administered, and at baseline and after 6 months of CBD treatment the Social Communication Questionnaire (SCQ), Aberrant Behavior Checklist (ABC), Vineland Adaptive Behavior Scales II (VABS-II), Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), and Children's Sleep Habits Questionnaire (CSHQ) was completed. Details of these measures are included in Chapter 4 of this dissertation. To better understand the possible relationship between these clinical responses and epileptiform discharges, 10 of the 33 enrolled participants had 24-hour EEG recordings taken at baseline and then again after 6 months of CBD treatment. As a note, only 10 participants were chosen to have EEGs performed due to regulatory and funding limitations of the present trial. The participants represented a range of seizure frequency and other varying baseline data to represent a range of participants.

This study was initially designed around the protocol of a Physician Expanded Access program agreed by the FDA and the Florida Department of Health. The aim was to better understand the safety and efficacy of CBD on seizure activity for children with intractable generalized epilepsy. Many drug trials do not supply all the necessary data to assist clinicians in making decisions about treatment options for overall assessment of quality of life outcomes. Ambitions of the study team have led to a more in-depth study objective, looking at the relationship between seizure activity, behavioral and functional changes, as well as EEG recordings to better conclude the effect of CBD on a child's brain and epilepsy in a more complete picture. Drawing more sound conclusions and observations will help to continue to build a foundation for CBD research and allow for future studies to ask more specific questions for improved drug treatment.

CHAPTER 3
EFFECT OF CANNABIDIOL TREATMENT ON SEIZURE ACTIVITY

Assessments of Efficacy on Seizure Activity

To assess the efficacy of CBD treatment, the primary outcome measure for this study was reduction in the monthly seizure frequency and severity. Seizures are considered one of the most problematic symptoms of epilepsy, as this abnormal burst of electrical activity in the brain often disrupts an individual's ability to function normally. In children with intractable generalized epilepsy this is especially challenging for cognitive growth and learning, as the seizures prevent consistently normal brain function and hinder development. In order to determine the impact of CBD on seizure activity, once participants were admitted into the study they received a seizure diary where the parent or caregiver was to record every time a seizure occurred and note what type of seizure it was. The seizure diary template, provided by the Epilepsy Foundation, is considered a routine practice for individuals with epilepsy and is commonly used in a clinical setting for tracking monthly seizure activity. The types of seizures recorded by the parents and caregivers were considered to be all generalized, affecting both sides of the brain - tonic-clonic (also known as grand mal), myoclonic, atonic, and absence.[66]

The general public most commonly knows of tonic-clonic seizures as they tend to be considered the most intense with full extension and shaking of the outer extremities and complete loss of motor control. Tonic-clonic seizures are generally very taxing on the individual, having residual side effects that include fatigue, body pain, headaches, or continued problems with movements, vision, or speech. Myoclonic seizures often occur in clusters and involve quick or sudden jerks in the muscles. Atonic seizures, also called drop attacks, are when there is an unexpected loss of muscle tone and the individual

loses motor control, often causing the person to fall over or for the head to drop suddenly. The most commonly occurring generalized seizures are absence, which are generally quick occurring seizures (less than 30 seconds) and usually include twitching in the face and rapid eye blinking. Most people do not realize that they are having absence seizures, which often occur several times throughout the day, and they tend to continue on with their activities, often having many episodes throughout the day. During the seizure, gaps of time are lost, so there are several gaps throughout each day. The experience is compared to that of a record skipping while playing a song.

Additional outcome measures recorded in the seizure diary were any adverse events that occurred over the course of the month and any use of rescue medication, such as diazepam (brand name Diastat). Over the course of the study, the patient's seizure diary was examined and logged by the study team after one, two, three, and six months of CBD treatment and compared back to the baseline period when no CBD was administered. The patient was instructed to keep all current AEDs at a steady state throughout the course of the study, only changing them if it was deemed clinically necessary by both the study's assigned neurologist and the participants personal prescriber. The means or medians and ranges of seizures were calculated for each individual patient at baseline and after 6 months of treatment. Due to such a large range of seizure frequencies, the median percentage change was calculated for the entire cohort. Percentage change was calculated at baseline, 3 months, and 6 months for all participants and each seizure type as:

$$\%\, Seizure\ Frequency\ Change = \left(\frac{3\ or\ 6\ month\ seizures - baseline\ seizures}{baseline\ seizures}\right) \times 100$$

Since the first month of CBD treatment was a titration period, it was determined that comparing seizure frequency after 3 and 6 months would provide a more accurate indicator of efficacy when compared to baseline. We hypothesized that seizure frequency would decrease within this population after CBD treatment was introduced, similar to that of previous studies completed in a similar nature. For statistical analysis, the Wilcoxon sign-rank test was used to compare the seizure frequencies between baseline, 3 months, and 6 months. Non-parametric permutation tests were conducted with one million permutations each to obtain empirical p-values. The significance level for all statistical tests was $p < 0.05$, with excellent normal approximation for this sample size.

Seizure Activity Results

Of the thirty-three children enrolled in the study, three were excluded from the analyses because they did not complete the full 6 months of the study. All three participants were withdrawn from the study due to efficacy results or because the measured outcomes did not meet their personal expectations. These three received at least 3 months of CBD treatment before they withdrew. Of the thirty (n = 30) children who completed having their seizures recorded for the full the 6-month trial, twenty-eight (n = 28) were at a maximum dosage of 25 mg/kg per day and the remaining two (n = 2) were at 20 mg/kg/day. The total number of seizures at baseline and after six months, with the percent seizure frequency change, is presented in Table 3-1. Responders to CBD treatment were considered to be any child who saw >50% reduction in monthly seizure activity after 6 months of treatment with their current AEDs.

The individual seizure results showed that 21 of the 30 were considered to be responders (n = 21) to the CBD treatment. Fourteen (n = 14) were high-responders,

with a reduction of >80% of monthly seizure frequency and three (n = 3) were completely seizure free. It is important to note that the parents of one participant gave their best estimate of seizure recordings, as the frequency was so high (~3900) that it became difficult to initially monitor all activity.

Table 3-1. Individual mean seizure frequency results and percent change after 6 months of treatment.

Patient no.	Age (Years)	Baseline Seizures	6 Month Seizures	Change (%)
1	8	25	3	-88.0
2	6	179	163	-8.94
3	8	140	33	-76.43
4	14	277	0	-100.0
5	16	238	44	-81.5
6	15	99	72	-27.3
7	13	9	2	-77.8
8	15	-	-	-
9	10	-	-	-
10	7	69	58	-15.9
11	11	15	2	-86.7
12	16	77	3	-96.1
13	7	33	0	-100.0
14	14	19	3	-84.2
15	13	-	-	-
16	9	20	2	-90.0
17	17	20	14	-30.0
18	15	469	35	-92.5
19	14	219	75	-65.8
20	14	26	4	-84.6
21	9	185	105	-43.2
22	13	65	13	-80.0
23	10	120	73	-39.2
24	11	176	5	-97.2
25	4	78	17	-78.2
26	2	183	88	-57.5
27	3	178	167	-6.2
28	16	45	8	-82.2
29	4	7	0	-100.0
30	7	28	8	-71.4
31	7	40	21	-47.5
32	8	3900	1230	-68.5
33	7	9	4	-44.4

The baseline median seizure frequency for all seizure was 69.0 (p=0.04)(range of 7 to 3900) and decreased to 15.0 (p=0.02)(range of 0 to 1230) after 6 months. The

median percent change in monthly seizures from baseline after the 6-month treatment period was -65.7% (p=0.02) for the entire cohort of participants. Due to the large range of reported seizures, we felt it was noteworthy to examine if there were any differences in percent reduction between those who started treatment with a high seizure rate compared to those who began the study with much fewer. The question being asked at this point was if those who have more or less seizures at the start have varying changes in seizure frequency compared to one another.

To do this we split the cohort of patients into three groups with ranges of starting monthly seizures between 4 to 40, 41 to 140, and 141 to 3900. Table 3-2 displays the results, where we see that there is no significant difference between the small groups, with those having between 4 and 40 seizures at baseline seeing a 67.9% decrease, those between 41 and 140 showing a 66.3% decrease, and those with much higher starting seizures between 141 and 3900 having a mean reduction of 63.4%. We can conclude it is appropriate to compare the entire group of participants together, as the starting number of seizures does not have an impact on the reduction of overall seizure frequency.

Table 3-2. Monthly median seizure frequency change for groups of participants with varying total starting seizures.

Starting Seizure Ranges	N	Change After 6 Months (%)	p
4 - 40	13	-67.9	0.04
41 - 140	9	-66.3	0.05
141 - 3900	11	-63.4	0.04

Individual seizure types were also noted in the seizure diary by the parents or guardians for each of the participants completing the 6-month trial (n = 30). The mean changes in frequency for each of the recorded seizure types are found below in Table 3-

3. There was an observed reduction in all four seizure types, with tonic-clonic decreasing from a mean of 11.9 per month (range of 0 to 78) at baseline to 2.5 (0 to 48) after 6 months of CBD treatment for a frequency reduction of 78.9%, myoclonic decreased from 17.0 (0 to 137) to 9.3 (0 to 108) for a 45.3% reduction, atonic frequency fell from 136.9 (0 to 3100) to 18.9 (0 to 980) reducing by 64.2%, and finally absence seizures which decreased from a mean of 53.5 per month (0 to 800) to 10.2 (0 to 250) for a total reduction of 81.0%. All statistical analysis revealed $p<0.05$ for each seizure type.

Table 3-3. Monthly median seizure frequency for each seizure type.

Seizure Type	Baseline Mean	3 Month Mean	6 Month Mean	Change After 6 Months (%)
Tonic-clonic	11.9	2.8	2.5	-78.9
Myoclonic	17.0	9.2	9.3	-45.3
Atonic	136.9	69.7	48.9	-64.2
Absence	53.5	15.2	10.2	-81.0

During the one-month baseline seizure recording, sixteen (n = 16) children went into a state of status epilepticus (SE), which is when uncontrolled seizure activity occurs for more than three minutes and rescue medication (diazepam) is used. SE is known to have high morbidity and mortality rate in children with intractable seizure activity, being one of the more dangerous results of uncontrolled epileptic activity. After 3-months of CBD treatment, seven (n = 7) patients (43.7%) had incidents of SE and then after 6-months of CBD usage four (n = 4) (25.0%) had noted these incidents.

Discussion of seizure results

After CBD treatment was introduced to the children enrolled in this study with intractable generalized epilepsy, there was a clear reduction in seizure activity. With >50% reduction considered to be the responder target, 70% of the participants who

completed at least 6 months of seizure tracking met this criteria of efficacy, with 47% having a majority or all of their seizures under control (80-100%). Ideally, an antiepileptic drug would completely subdue all seizure activity, though the Food and Drug Administration requires a minimum of 25% of tested patients to have more than 50% seizure reduction, along with other safety guidelines, in order to be considered successful treatment and eventually approved.[67] The results of this study, taking into consideration the smaller population size, easily meets all expected efficacy outcomes for FDA drug approval while showing few side effects, of which will be discussed in Chapter 6.

To better understand the significance of efficacy of this CBD treatment, we can compare the seizure reduction results to that of two of most commonly prescribed AED's for children with generalized epilepsy, lamotrigine and topiramate.[68] During the open phase of a similar study,[69] 27 children with intractable generalized epilepsy received lamotrigine for an average of five months. At the end of this study phase, 7 (26%) had greater than 50% seizure reduction with one having >75% reduction and one other child being completely seizure free. It is relevant to note that 20 of the children in the study were diagnosed with Lennox-Gastaut, which was an exclusion criterion for our own study. Finding other comparable studies involving the use of AEDs specifically for children with intractable generalized epilepsy was challenging, especially examining the efficacy of topiramate in this population. The most analogous study involved 106 children who were administered topiramate as part of an open label trial for their generalized seizure activity.[70] After 6 months of treatment with topiramate, 70 (79.6%) had >50% seizure reduction and 13 (14.8%) were completely seizure free. Paralleling

these results with that of our own study, we noted that CBD is just as effective, if not more so, for reducing seizure frequency in children with intractable generalized epilepsy. CBD for use with intractable patients also proved to be comparable to the efficacy of popular AEDs for general epilepsy treatment.

Looking at the effect of CBD on individual seizure types, we see that all four reported in this study saw a major reduction in both number and severity. The greatest reduction was observed in both tonic-clonic and absence seizures with eleven individuals becoming seizure free from each (50.0% and 64.7% respectively). Reduction in these two seizure types is significant for several reasons. Tonic-clonic seizures affect the entire body, causing the individual to have muscles stiffen, loss of consciousness, biting of the tongue or cheek, loss of airway control and oxygen, followed by rapid and violent jerking of all extremities with possible loss of bladder or bowel control. Tonic-clonic seizures often last a few minutes, leaving the individual confused, agitated, and exhausted. Some lasting more than 5 minutes often requires emergency treatment and can cause lasting brain damage or even death in severe cases. For children, uncontrolled tonic-clonic seizures represent a great risk, as the intensity and vehement nature of the seizure on the developing brain and body can result in constant exhaustion, spasms, and permanent debilitation. Reducing the number of tonic-clonic seizures experienced by a child with intractable epilepsy, as seen after treatment with CBD, is a significant step forward in improving the child's quality of life and minimizing the risk that these intense seizure types can have.

Absence seizures, while not as intense as tonic-clonic, are often very disruptive of a child's day-to-day functionality. Lasting a few seconds, sudden irregularity in

neuronal activity causes short electrical bursting that results in the child to become very still and have a vacant stare, sometimes accompanied by eye fluttering. Absence seizures do not often result in physical harm to the individual, but they generally occur much more often and constantly interrupt a child's learning and development with sudden stops in activity. Most children grow out of this seizure type, with the exception being those with intractable epilepsy where the interruption continues. After CBD treatment, children experienced a major decrease in absence seizure activity with a reduction of 81.0% in median frequency. A similar study compared the efficacy of valproate acid and lamotrigine, two common AEDs, on absence seizure reduction.[71] In that study each drug was administered to nineteen (n = 19) different children with juvenile absence seizures for 12 months in an open-label parallel group design. At the end of the study, 52.6% of children taking lamotrigine were completely free of absence seizures and 68.4% were free after treatment with valproic acid. In our study, 64.7% of children were free of absence seizure activity after 6 months of CBD treatment. This is a comparable result to what was seen by both FDA approved AEDs (Table 3-4), and it is certainly relevant to note that the children in the mentioned study were not diagnosed with intractable generalized epilepsy, showing that CBD is also effective on absence seizure activity in a cohort of patients, particularly where these other medications are not a reasonable option. It has been noted in a review of AEDs that effective reduction or elimination of absence seizures is commonly due to successful blocking of calcium channels that these compounds use as a mechanism of action. The significant decrease in absence seizures after 6-months of CBD would also allude to a mechanistic connection of this cannabinoid to the control of calcium channels in the brain.[71]

Table 3-4. Comparison of common AED efficacy in absence seizures to CBD.

AED	Dosage Range (mg/kg/day)	Study Length (Months)	Number of Children	Number of Children Seizure Free	Percent of Seizure Free Children
Lamotrigine	20 - 30	12	19	10	52.6%
Valproic Acid	2 - 11	12	19	13	68.4%
Cannabidiol	20 - 25	6	17	11	64.7%

Use of cannabidiol by children with intractable generalized epilepsy resulted in a clear clinically significant reduction in seizure frequency and severity. With seizure control being the primary outcome measure of this study, an effective response was measured at >50% reduction, where 70% of the children enrolled responded to CBD when it was added to their other concomitant drugs. The efficacy of CBD, as shown by this study's result, appears to be promising for those children with no other feasible means of seizure control, especially for those who ended completely seizure free. Reduction in the number of seizures, the intensity of those experienced, as well as the number of SE events is a major stride forward in examining the efficacy of CBD as a treatment alternative for all seizure types. These results are comparable to other open-label studies involving currently FDA approved AEDs. While >50% reduction is considered an ideal responder rate for a traditional study involving new AEDs, it should be considered that for a target cohort of patients with intractable seizure activity, even a reasonable reduction of activity of >25% can be significant to quality of life improvement and is relevant in a clinical setting when there are no other treatment options.

The major limitation of this study, as it specifically relates to seizure frequency and recording, was the inconsistency of who was monitoring and recording seizure activity, as well as how it was observed, from month to month. With children being seen

by nurses, physical therapists, teachers, and others, as well their parents or guardians, the reported seizure activity is not always consistent from person to person. This is especially true when it comes to denoting a specific seizure type as experience with seizure identification from one individual to another can vary significantly. The children in the study also experienced seizure activity at various times of day where it could be missed by the recorder, and sometimes a child had so much activity it was hard to separate events or count them all. Ideally, each participant would have the same person monitor their activity and use the same standards as established by the study team for both type and frequency measures. Another limitation is the varied use of AEDs by the study participants. Each individual was on a completely difference combination and dosage of AEDs, and with the participants able to adjust their dosages after 3 months of CBD treatment, it creates difficulties in making consistent comparisons over time within the results of the participants.

Video monitoring during sleep would also assist in capturing all seizure activity and should be utilized in future studies. The other limitation that could have influenced the accurate measure of seizure activity is that this is an open-label study where a placebo response is a strong possibility. This topic will be touched on in greater detail in Chapter 7 of this dissertation, but while the intention of this study was to focus on efficacy of CBD as an add-on to other AEDs for children with intractable epilepsy, a randomized, double-blinded controlled study would assist in determining the true clinical efficacy of the drug. The initial conclusion can be made that CBD is generally effective in the control of intractable seizures of all types, especially those that can be most debilitating to the developing brain of a child.

Data Collection and Measures

Many clinical studies evaluating the efficacy of AEDs typically focus on seizure frequency reduction or control as the only outcome measure. Of the few open-label trials involving the use of CBD as a treatment option, most follow this methodology as well. Therapeutic and efficacy decisions based solely on seizure control are not an accurate representation of patient's overall quality of life. The specific aim of these clinical assessments and measures was to determine if there were any parallels between seizure frequency changes and any variations in each child's daily functioning, behavior, and quality of life after CBD was added to their medicinal regimen. Children with severe epilepsy conditions frequently experience major regression in cognitive function and behavior as a result of seizure activity, especially those with drug-resistant epilepsy. Clinicians have long acknowledged that uncontrolled seizure activity causes disruptions in daily functioning, which often leads to educational limitations, social communication problems, disruptive behavior, irritability, noncompliance, motor deficits, sleep deprivation, and more, all negatively impacting the child's quality of life as well as causing added stress to the lifestyle of parents, guardians, and family members.

A number of parents who have administered oral CBD extracts to their children for seizure treatment have anecdotally reported additional improvements in mood, alertness, language, and motor skills.[72] While these expressed improvements are significant to note because of CBD treatment as it alludes to other possible improvements, anecdotal parent reports can be skewed from personally desired outcomes or even media implications. To better assess how effective CBD can be as a

therapeutic treatment, in our study, we utilized clinically validated questionnaires and measures in combination with anecdotal reports from parents or guardians. The valuations used were the Social Communication Questionnaire (SCQ), Clinical Global Impression-Improvement scale (CGI-I), Aberrant Behavior Checklist (ABC), Vineland Adaptive Behavior Scales II (VABS-II), Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), and Children's Sleep Habits Questionnaire (CSHQ). We believe that this unique addition of behavioral and functional assessments to the primary outcome measure of seizure frequency would provide a better overall evaluation of CBD treatment on the quality of life of children with intractable epilepsy. It is our hypothesis that the measures utilized in this study would show an overall improvement in behavior and quality of life after CBD treatment is introduced, as indicated by previous surveys and reviews noting such by parents and guardians.

Social Communication Questionnaire (SCQ)[73]

The Social Communication Questionnaire is typically used to screen for autism spectrum disorders in children. It is also a reasonable and beneficial measure for other childhood deficits, as the behavioral characteristics associated with epilepsy are often very similar to those characterized with autism. The SCQ consists of 40 yes or no questions answered by parents or guardians that focus on social interactions, functioning, and communication skills. This questionnaire looks at a child's behavior over the most recent 3-month period and was used in this study to assess the initial social deficits that the participants were experiencing prior to treatment with CBD. Many clinicians and psychologists use this tool to assess symptoms and determine the best course of intervention or treatment. While the form can be used for all children whose

mental age exceeds 2 years, it is most beneficial for those over the age of 4. For this reason, we excluded all children in this study under the age of 4 in the analysis of the SCQ scores over time. A total SCQ raw score greater than 15 is often suggestive of autistic characteristics and social deficits. The SCQ was administered for this study only at baseline, as it was not considered an outcome evaluation.

Clinical Global Impression-Improvement scale (CGI-I)[74]

The CGI scales are often used in treatment studies of patients who suffer from mental deficits to measure both severity of the deficit and any changes over time as a result of the treatment response. It is a brief assessment of a clinician or trained specialist's perspective of patient's overall function before and after beginning study treatment and has been shown to correlate well with standard research drug efficacy scales.[75] The clinician performing the CGI takes into consideration a patient's history, symptoms, behavior, and how the symptoms impact the ability to function. The Improvement Scale (CGI-I) is a 7-point scale that specifically assesses how much a patient has improved or declined relative to when they started the study. A clinician with epilepsy expertise used the CGI-I scale at baseline and then at every clinical visit up to 6-months of CBD treatment to record any changes in the severity of the participant's deficits over time. A study member who is blinded to each patient's treatment or response typically performs the CGI-I assessment, but due to the open-label nature of this present study this feature was not included in the recording of monthly scores. For this reason the CGI-I was used as a characterization tool rather than a direct measure of deficit improvement. While several studies have performed these scales as an

unblinded assessment, it is important to note this as it could have had an effect on the strength of the results when comparing the scores over time.

Aberrant Behavior Checklist (ABC)[76,77]

The ABC is a set of scales that measures any symptoms or disturbances in young children with severe behavior problems such as aggression, disruption, and psychiatric conditions. It classifies and monitors the severity of these chronic behavior problems over 5 domains: Irritability, Agitation, & Crying; Lethargy/Social Withdrawal; Stereotypic Behavior; Hyperactivity/Noncompliance; and Inappropriate Speech. These disruptive behaviors, common in children with epilepsy, can interfere with daily social interactions and living skills, limiting any interventions that may be administered by caregivers. Ongoing generalized seizure activity often interferes with the development of a child's living skills and can cause physical discomforts, resulting frustration and exasperation. The lower the score measured with the ABC, the better the child's behavior is. The ABC was administered at baseline and then again after 6-months of CBD treatment.

Vineland Adaptive Behavior Scales II (VABS-II)[78]

The Vineland test is useful for assessing the ability of a patient with developmental delays or impairments to perform personal and social skills used in everyday life. The test aids in diagnosing and classifying various disabilities and is one of the most clinically used measures for tracking changes in these impairments after intervention. The VABS-II assesses daily living skills in a number of functional domains. There is also a Motor Skills domain that is available to prescribers, but it was not utilized in this analysis. The VABS-II was verbally administered to parents or guardians at

baseline and again after 6-months of CBD treatment to determine any progress or regression in their child's disabilities. This assessment was performed by a study member who was blinded to the patient's treatment and their seizure frequency response to CBD.

Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)

The QOLCE is a multi-faceted parental questionnaire that is used to evaluate the overall quality of life for children with epilepsy. It asks over 76 questions relating to daily living and used to assess how epilepsy, in comparison to children without deficit, affects a child's everyday life. It covers several domains, totaling 16 subsections, including physical ability, social activity, cognition, behavior, emotional stability, and overall health. Scores are calculated by adding up the scores of each subsection and then dividing by 16. A higher overall score is typically associated with a better quality of life and living skills. A change in score over time after treatment can assist in determining efficacy of the intervention. Each child's parent or guardian completed the QOLCE questionnaire at baseline and again after 6-months of CBD treatment. A mean QOLCE score was calculated for the entire cohort of patients.

Children's Sleep Habits Questionnaire (CSHQ)[79,80]

Epilepsy and resulting seizure activity can often negatively impact a child's sleep habits and cause difficulties with sleeping. The CSHQ is a parent-reported tool for addressing many characteristics of sleep including duration, anxiousness, disruption, night waking, daytime sleepiness. Fifty-two questions are asked with 33 of them scored on a 1 to 3 scale and totaled based on a set rubric. Any score of a 41 is commonly used as a cutoff score to indicate sleep problems that can be disruptive to daily living. The

CSHQ was administered to each child's parent or guardian at baseline and then again after 3-months and 6-months of CBD treatment.

All assessments were examined by a biostatistician using an analysis of variance (ANOVA) where an effect size above 0.30 was considered to be significant. Along with questionnaires and collected behavior measures we also collected anecdotal changes in each child's daily living and quality of life, as reported by parents at each clinical visit, detailing anything they have noticed after 6-months of CBD treatment. An IQ test was administered at baseline with seven (n = 7) of the thirty participants completing the study having an IQ >70, considered a normal cutoff score. The subjective results were combined with all quantitative measures as well as seizure frequency and responder rates to draw comparisons and conclusions about the overall efficacy of CBD on a child's functional and behavior changes throughout the length of study.

Behavior and Quality of Life Results and Discussion

Of the thirty-three children enrolled in this study, thirty (n = 30) completed all behavior questionnaires and examinations at baseline through 6-months of CBD treatment. For the SCQ and CSHQ, twenty-eight (n = 28) of the children's results were considered in the analysis as only those above the age of 4 years old could be considered for these screening techniques. As each of the study participants received a known dosage of CBD as part of an open-label trial, analysis was performed on the entire study population and then separated for the appropriate questionnaires by those with >50% seizure reduction, <50% seizure reduction, IQ scores >70, and IQ scores <70. The intent was to see if the SCQ resulted in scores denoting a deficit associated with all participants, as well as if there were any notable differences within the cohort for

those who had shown varying improvements in seizure frequency or had started with higher cognitive ability.

Table 4-1. SCQ scores recorded at baseline.

Subject Characteristics	N	Baseline Score
Seizure Reduction >50%	20	19.3
Seizure Reduction <50%	8	18.1
IQ >70	7	15.1
IQ <70	21	20.7
All	28	19.0

Table 4-1 displays the results of SCQ scores recorded at baseline before CBD treatment was introduced into each child's daily regimen. For all 28 participants whose parents completed the SCQ, the change the median score at baseline was 19.0, which would indicate that this cohort of participants largely faced social deficits. When separated by responder rates, those who had a >50% decrease in median seizure frequency (n = 20) had an SCQ score of 19.3 and those with <50% median seizure reduction (n = 8) had a score of 18.1 at baseline. This shows that there is no significant difference in initial social deficits between those who would eventually have a response to CBD treatment or those who had <50% decreases in seizure frequency. Seven (n = 7) children had an IQ score >70 and had a score of 15.1 on the SCQ and the remaining twenty-one (n = 21) with IQ scores <70 had the most severe score of 20.7. Here we see that a lower IQ score corresponds to a lower SCQ score, which is something that would be expected from these assessments. At baseline, seven (n = 7, 25.0%) children had been given an ideal score of 14 or below on the SCQ.

All thirty (n = 30) children completing the 6 months of CBD treatment had CGI-I results recorded after 3 months and at the end of the study. The CGI-I was completed by a physician with expertise in neurology, and specifically with epilepsy. The physician rated the child's response to the CBD treatment by giving one of seven ratings from 'Very Much Worse' to 'Very Much Improved' in comparison to their condition at baseline. Table 4-2 shows the results of the CGI-I where participants received a rating of either 'Much Improved' or 'Very Improved'. To receive this rating the patient would have to show signs of improvement in regards to symptom severity, functional ability, and overall improvement in health compared to the previous visit. Out of all 30 children completing the study, thirteen (n = 13, 43.3%) showed improvement after 3 months and then by the 6 month time period, nineteen (n = 19, 63.3%) had improved. None of the children saw regression in the CGI-I, with no ratings given below 'No Change'. When separating the cohort of patients by their seizure responder rate, of those who had >50% reduction in seizure frequency (n = 21), twelve (n = 12, 57.1%) showed improvement after 3 months and nineteen (n = 19, 81.0%) after 6 months.

Table 4-2. Children with a CGI-I rating of Much Improved or Very Improved.

Subject Characteristics	N	No. of participants at 3 Months	No. of participants at 6 Months	Percentage of Children at 6 Months	Effect Size
Seizure Reduction >50%	21	12	17	81.0%	0.43
Seizure Reduction <50%	9	1	2	22.2%	0.32
All	30	13	19	63.3%	0.48

Of the nine (n = 9) who had <50% reduction in seizure frequency, one (n = 1, 11.1%) had been rated as improved after 3 months and two (n = 2, 22.2%) had received

this rating after 6 months of treatment with CBD. It is important to note that, with the CGI-I, there are no standard guidelines for completing the ratings and that they are based solely on the physician's judgment. Due to there being 3-month breaks between when CGI-I ratings performed, clinical notes at each visit were important in order to capture an accurate rating determination.

The Aberrant Behavior Checklist was completed at baseline and 6-months by the parents or guardians of all thirty children (n = 30). The ABC was separated into four sub-domains: Irritability, Social withdrawal, Stereotypical behavior, and Hyperactivity. A lower score is considered to be an improvement in behavior. Table 4-3 shows the mean ABC scores for each domain and the change at baseline and after 6-months with calculated effect size.

Table 4-3. ABC mean scores and sub-scores after 6-months.

ABC and Sub-domains	Seizure Reduction <50%	Seizure Reduction >50%	All	Change	Effect Size
Irritability					
Baseline	27.9	24.9	26.3		
6-Months	17.2	11.6	14.4	-11.9	0.34
Social withdrawal					
Baseline	13.6	17.2	16.6		
6-Months	12.0	12.8	12.6	-4.0	0.33
Stereotypical behavior					
Baseline	7.1	7.7	7.4		
6-Months	7.2	6.9	7.1	-0.4	0.19
Hyperactivity					
Baseline	29.8	33.1	31.5		
6-Months	23.4	21.5	22.5	-9.0	0.43
Inappropriate Speech					
Baseline	3.4	3.2	3.4		
6-Months	3.2	2.9	3.2	-0.3	0.26

After 6 months of CBD treatment the participants saw a 45.9% decrease (26.3 to 14.4) in Irritability scores, a 24.1% decrease (16.6 to 12.6) in Social Withdrawal, a 4.1% decrease (7.4 to 7.1) in Stereotypical Behavior, a 28.6% decrease (31.5 to 22.5) in Hyperactivity, and finally a 5.9% decrease (3.4 to 3.2) in Inappropriate Speech. A desired effect size of 0.5 is considered meaningful for detecting an effect of treatment within each of the subdomains.

Irritability and Hyperactivity showed the most clinically significant differences in the mean ABC scores after the children's use of CBD. Comparing the differences in ABC scoring as it relates to seizure responder rates, those who had a reduction in seizure frequency >50% (n = 21) saw a 53.4% decrease in Irritability scores, 25.6% decrease in Social withdrawal, 10.4% decrease in Stereotypical behavior, 28.6% decrease in Hyperactivity, and a 9.4% decrease in Inappropriate speech scores. Those who had <50% reduction in seizure frequency (n = 9) showed a decrease of 38.4% in the Irritability domain score, a 14.8% decrease in Social Withdrawal, a 1.4% decrease in Stereotypical Behavior, 21.5% decrease in Hyperactivity, and a 5.9% decrease in the Inappropriate Speech scores. Here we saw that responders with >50% reduction had a greater mean change in scores for each of the ABC domains, with Irritability and Hyperactivity again showing the most significant improvements with both groups.

The Vineland (VABS-II) was scored at baseline and after 6-months of CBD treatment for the Communication, Daily Living Skills, and Socialization domains. The change in mean scores was calculated for all participants (n = 30), those with seizure frequency reduction >50% (n = 21), and <50% seizure frequency reduction (n = 9). A higher VABS-II score is considered an overall improvement in function and daily living.

The Communication domain saw a 16.2% increase in mean scores (54.28 to 63.08), Daily Living Skills an increase of 15.4% (56.00 to 64.67), and an increase in Socialization scores of 18.5% (58.47 to 69.32) for all children in the study. All three subdomains saw a significant improvement across the entire group.

Across all three domains, the participants who had a higher seizure frequency response rate also had a slightly higher improvement in scores, though there was not a significant difference between those who had >50% reduction in seizure frequency and those with <50% reduction. Socialization saw the biggest difference between these groups, increasing by 19.9% (58.63 to 70.32) for children with >50% seizure frequency reduction compared to an increase of 14.7% (58.04 to 66.56) for those with <50% seizure frequency reduction. When comparing participants using IQ scores above or below 70, those who had an IQ <70 at the start of CBD treatment had a greater improvement in scores compared to those with IQ scores >70. The results of the groups separated by IQ's were not statistically significant, though the notable trend does match those shown by other measures used in this study where participants with >50% reduction or an IQ <70 having the greatest improvement in scoring.

Table 4-4. VABS-II domain scores after 6-months.

VABS-II Domains	Seizure Reduction <50%	Seizure Reduction >50%	IQ <70	IQ >70	All	Change in All	Effect Size for All
Communication							
Baseline	55.01	53.87	52.07	56.45	54.28		
6-Months	62.34	63.86	62.94	64.88	63.08	+8.81	0.42
Daily Living Skills							
Baseline	55.66	56.23	54.21	59.44	56.00		
6-Months	64.02	65.12	63.72	66.38	64.67	+8.67	0.39
Socialization							
Baseline	58.04	58.63	57.21	60.45	58.47		
6-Months	66.56	70.32	68.34	70.11	69.32	+10.85	0.44

Parents or guardians for all participants completing 6 months of CBD treatment at baseline and at the end of the trial completed the Quality of Life for Children's Epilepsy questionnaire. Changes in mean scores for all patients (n = 30), those who had >50% reduction in seizure frequency (n = 21), <50% (n = 9), an IQ score >70 (n = 7), and an IQ score <70 (n = 23) are shown in Table 4-5. The mean QOLCE score improved from baseline by 13.9% (53.4 to 60.8) after 6 months of treatment with CBD in conjunction with the patient's other AEDs. There was an increase in mean scores of 14.1% for patients with >50% seizure frequency reduction, +13.4% for those who had <50% reduction, +11.35 with patients who an IQ above 70, and +23% for those who scored <70 on the IQ test. The effect size proved significance in treatment efficacy for all patients as well as the separated responder and IQ groups.

Table 4-5. Change in mean QOLCE scores after 6-months.

Subject Characteristics	Baseline Score	6 Month Score	Change	Effect Size
Seizure Reduction >50%	53.4	60.8	+7.4	0.45
Seizure Reduction <50%	50.1	56.8	+6.7	0.33
IQ >70	55.5	61.8	+6.3	0.23
IQ <70	46.8	57.6	+10.8	0.30
All	52.1	59.3	+7.2	0.56

Finally, the mean CSHQ scores were analyzed, determining if there were any fluctuations in sleep before and after CBD treatment. The CSHQ was calculated as a total score and then for several sub-groups to better understand the specific changes occurring with the child's sleep as a result of CBD being introduced. Twenty-eight (n =

28) parents or guardians completed the CSHQ, with the remaining two of those who had completed the study being too young to appropriately analyze the scores (<4 years of age). A lower score typically indicates an improvement in sleep and a reduction of disturbances after the treatment period. Table 4-6 shows a 14.1% decrease (68.61 to 6013) in overall CSHQ scores after the 6-month trial was complete. Of the individual CSHQ subgroups, Bedtime Resistance (-27.1%, 8.92 to 7.02), Sleep Duration (-68.2%, 5.14 to 3.25), and Night Wakings (-62.5%, 5.33 to 3.28) saw the greatest improvement. Daytime Sleepiness was the one sub-group that saw an increase in mean score of +12.0% (10.62 to 11.89), signifying a regression in this particular area of the child's sleep habits. It is important to note that the mean total score for the entire cohort of participants was still above the cutoff score of 41, indicating that deficits were still prevalent in the children's sleep habits, though the trend in improvement was still significant to overall quality of life.

Table 4-6. Children's Sleep Habits Questionnaire mean scores.

CSHQ & Sub-groups	Baseline	6-Months	Change	Effect Size
Total	48.18	41.84	-6.34	0.42
Bedtime resistance	8.92	7.02	-1.90	
Sleep-onset delay	1.83	1.72	-0.11	
Sleep duration	5.14	3.25	-1.89	
Sleep anxiety	5.71	5.11	-0.60	
Night wakings	5.33	3.28	-2.05	
Parasomnias	9.36	8.42	-0.94	
Disordered breathing	2.78	2.66	-0.12	
Daytime sleepiness	10.62	11.89	+1.27	

Parents or guardians of all thirty children completing the study, as well as from those who opted to be removed from the study before completion of the 6-month trial (n = 33), reported any general changes or improvements in their child's behavior over the course of the study. The results of these anecdotal reports of improvements are shown

in Table 4-7. The most significant improvements reported were with Attention (n = 17, 51.5%), Mood (n = 19, 57.6%), Visuospatial (n = 13, 39.4%), and Communication (n = 13, 39.4%). What was also substantial to note was that twenty-seven (n = 27) children were reported by parents or guardians to have an improved overall Quality of Life (81.8%) in comparison to before they started taking CBD in conjunction with their other AEDs.

Table 4-7. Parent Reported Improvements.

Reported Improvement	N	% Showing Improvement
Memory	9	30.0
Attention	17	51.5
Visuospatial	13	39.4
Mood	19	57.6
Motor	10	30.3
Appetite	12	36.4
Sleep	10	30.3
Communication	13	39.4
Energy	11	33.3
Quality of Life	27	81.8

Discussion of Behavior and Function Results

A variety of questionnaires and examination tools were used in this study to assess the effect of CBD on a child's behavior, ability to function, and general quality of life, many of which were compared with any changes in seizure frequency. The intent was to use these several tools to capture an overall understanding of the potential effects that CBD can have on a child's performance and state of living – a unique area of interest that has yet to be examined in other CBD studies, but is significant towards evaluating the complete safety and efficacy of the study. Across all measures, there was either a significant improvement in scores compared to those collected at baseline or there was, at a minimum, a trend in scores that would indicate an improvement over

time. While the Social Communication Questionnaire is not commonly used as a measure for children with epilepsy, there are many similar behavioral deficits between children with epilepsy and those with autism.

The results of the CGI-I scores throughout the study show a significant improvement in overall function of many the participants, with 63.3% scoring 'Much Improved' or 'Very Improved'. We also note the results corresponding to those of the SCQ, with patients who had >50% reduction in seizure frequency showing the significantly greater improvement (81%) compared to those who had <50% reduction (22%). The improvement in CGI-I scores for those not considered responders should not be overlooked, however, as even a 'Much Improved' score for those with little drop in seizure frequency likely still means an improvement in quality of life for that child. While it is valuable to have a physician with epilepsy expertise evaluating the child's function over time, this tool is subject to user-error. Typically, the CGI-I is used to assess changes after 7 days, with the time points collected in this study considered to be very far apart for normal CGI-I use. Also, many studies prefer to use a blinded physician who does not have an interaction with the participants or parents or guardians outside of the CGI-I scoring period. It is important to note that these factors could lead to a bias and inaccurate scoring. That said, the improvements noted by the physician are so significant, that it is safe to say there is a valuable change in function over time for the children on CBD treatment.

The ABC provided more specific insight into the behavioral changes that occurred with children in the study. Again, we saw a trend in improvement in all measured domains, with Irritability and Hyperactivity having the greatest change and

significance. Many children with epilepsy and seizures often display poor behavior, being short tempered, having uncontrolled mood changes, or complaining of head pain and pressure. Most physicians attribute this to the over excitability of the child's brain and the intense generalized seizure activity they frequently experience. The reduction in ABC scores for the Irritability and Hyperactivity correspond to behavioral changes we would expect to see when seizures are reduced or better controlled, directly correlating to improved seizure frequency. Those participants who had a significant seizure response of >50% also saw the greatest decrease in all sub-domains compared to those with <50% reduction, with the exception of Inappropriate Speech, which was not considered clinically significant for this trial's population. We continue to observe improved scoring for all participants having a seizure frequency response to the CBD. Relying on parent/guardian responses is, of course, a limitation as responses can be biased when not blinded. Behavior that is disruptive to day-to-day activities can interrupt learning and social interactions that help the child develop and normally function. Reducing these noncompliant and challenging behaviors could positively effect both the child's ability to function and learn in social settings as well as improve the quality of life of family members and those around them who are faced with the challenges of managing the demands these behaviors put on them.

Patients recorded an improvement in scores in all three of the Vineland-II domains; Communication, Daily Living Skills, and Socialization. The Socialization domain saw the greatest improvement with a median score after 6-months of CBD treatment being 18.5% higher than when completed at baseline. The Vineland-II results correspond to those captured with the SCQ, with both showing an improvement in

social skills and the child's ability to communicate. Typically, a jump in domain scoring of greater than 5 points would be considered a substantial improvement,[81] adding to the significance of a median 8+ point increase for the participants in this study after CBD use. The Socialization domain had the biggest differences in scoring between those who had >50% seizure reduction compared to those with <50%, with responders scoring 5.2% higher. Responders had the greatest scoring improvement in all domains of the Vineland-II, but were much closer to the to the median increase in score of those with <50% response for the Communication and Socialization domains. We also analyzed the sub-domains for all participants completing the Vineland-II to better establish what specific areas of these domains the improvements are occurring in. As noted in the results, the Receptive and Expressive sub-domains within Communication and the Interpersonal and Play and Leisure sub-domains within Socialization had the largest increases in scores. The higher scores in these particular sub-domains correspond to the improved scores in the SCQ and correspond with some of the anecdotal parent reports of better communication.

The QOLCE scores also reflected the movement of the participants towards overall improvement, with a 13.9% increase in median scores for all participants, representative of an improved quality of life since starting the study. Children who had seizure reduction >50% after 6 months as well as those who had an IQ <70 had the greatest overall improvement in QOLCE scores, with the largest difference being between the IQ groups, where those with an IQ <70 scored 4.5 points higher than those with an IQ >70. This result matches with the other measures performed in this study. A similar study aimed at capturing the QOL scores for children with epilepsy saw similar

scoring ranges with a mean QOL score of 62.62 (SD = 21.32),[82] comparable to this studies QOL score of 52.1 (SD = 12.61) at baseline. While this does indicate the study team performed an accurate measure of scoring, it is significant that participants in this study, who improved with a mean score of 59.3 after 6 months of CBD treatment, are still within a range of deficit as a result of their epilepsy. The QOLCE provides valuable insight to a child's overall quality of life and it shows, even with improvement and better medications, inclusive care of these patients needs to be focused on the child's overall health and wellbeing and not just control of seizure activity.

Sleep disruption is common among children with epilepsy, and especially those who have uncontrolled seizure activity. Loss of sleep or poor sleep often leads to impairment of daily functioning, poor cognitive development, radical changes in mood, behavior, and even loss of attention and learning (Souders et al 2009). Being overly tired often leads to an increase in seizure activity, creating an ongoing cycle of poor quality of life for these children. The CSHQ was performed at baseline and after 6-months of treatment to see if CBD would have an effect on the participant's overall sleep. There was an improvement after CBD was introduced, with a decrease in mean overall scores of 14.1% for all patients. After analyzing the sub-groups of the CSHQ, Bedtime resistance, Sleep Duration, and night waking showed the most improvement. The scores of these sub-groups were very close, or even better, to those of typically developing children.[83] While the other sub-groups showed a trend towards better sleep, there was minimal significance between the scores. Improvements in sleep have a chain reaction on other areas of a child's life such as cognition, mood, function, and health. One area that deteriorated for the participants was Daytime sleepiness, which

increased in score by 12.0%. One possible reason for this increase could be from the reported lethargy and tiredness that many parents have noted as an adverse event when introducing CBD to their child. This will be discussed more in Chapter 6, but should not go unnoticed as daytime sleepiness can also relate to social and learning deficits.

Overall, there is a significant amount of evidence, provided by the questionnaires and tools used in this study, that show that cannabidiol has a positive effect on behavior, daily functioning, and overall quality of life of children with intractable generalized epilepsy, in conjunction with improved seizure frequency. While the calculated significance of many of these measures is limited and more data is certainly needed to draw more concise conclusions, this is one of the first studies to attempt to capture any behavioral or functional changes with children who are taking CBD for their epilepsy and the trend towards improvement is prominent. Seizure reduction remains the focal point of most AEDs, as well as trials involving CBD, as they have the most direct impact on a child's health. That said, the effect of AED's on a child's overall quality of life cannot be ignored and the decisions of parents and physicians for choosing the appropriate mode of therapy or medication should not be solely focused on seizure frequency, as improvements in social skills, learning, and behavior are just as significant. Interventions designed to help with behavioral and emotional progress as well as seizure control should be an important goal of any form of epilepsy management.

As shown by a number of measures used in this study, patients who had a greater response to CBD in the form of seizure frequency reduction also displayed the

greatest improvement in questionnaire scores for a majority of assessments and their included domains. The most direct conclusion of this result would be that the significant reduction in seizure frequency is also leading to and allowing for perceptive and behavioral changes to occur in these children. Those who benefit in one area of seizure frequency also tend to benefit the most in other areas of measure. What we are likely seeing is a corresponding effect. When there is better neuronal control in the brain and less disruption in the form of over activity as a result of the CBD, it allows for the child to regain some of the lost cognition and for adaptive learning traits to be reestablished and advancements towards normal function to be made. Those participants who had <50% reduction in seizures did still see an overall improvement from baseline with the study measures, if not as significant, which would again show that CBD still has a positive effect on these children who have no other viable treatment options. Patients with a baseline IQ score of <70 had greater improvements in scores when compared to those who had a >70 IQ. While the population size was not large enough to denote clinical significance, it is a development worth exploring. Likely this result is due to the circumstance that the patients with a lower intellectual ability have greater potential for cognitive improvement compared to those who were already at or above a normal IQ.

Parent reported improvements have been the most common form of measures of improvement or regression for current CBD studies. It is interesting to compare some of these reports with the clinically used assessments to determine any correlation or significance. Parents and guardians of children in this study saw a significant improvement in their child's mood, attention, communication, and especially quality of life. The improvement in mood (51.5% of children) does correspond to what was seen

with the ABC results, which saw a decrease in Irritability and Hyperactivity. In general, children who are feeling better and who have better control of their behavior and emotions appear to be, or report being, happier and have better moods. The 51.5% of children reportedly having an improvement with attention (cognitive engagement) could also be matched with the ABC, and especially with the Vineland-II where children scored higher in the Receptive and Play and Leisure sub-domains. Better communication that was reported by parents (39.4%) also corresponds to the higher Communication domain scores of the Vineland-II. These noted changes could also be a result of better sleep quantified by the CSHQ and reported by 30.3% of parents, where progress in daily function often result. The Quality of Life results are what might be most intriguing. There was a clear improvement as denoted by the QOLCE and CGI-I scoring for all participants, showing an improvement of 13.9% and 81% in scores, respectively. This matches well with the 81% of parents reporting that they believed their child's Quality of Life had improved after 6 months of CBD treatment. While it is difficult to make a direct correlation between the parents reported improvements to those seen in the quantitative measures used in this study, it is still relevant to note that similar trends are seen in both.

Parent reported data is always subject to debate over accuracy and should certainly never be used as a direct measure of efficacy, especially in a population of children who have very few treatment options and little room for recovery. Parents can often be bias by the hope that a new medicine or therapy can and is having a positive, or even negative, effect on their child. Other studies have shown the effect that CBD as a treatment for epilepsy and seizures can have on those reporting results anecdotally.

For example, one such study reported the response of patients who received CBD-based medication in the state of Colorado[72]. Of those who lived in Colorado, 22% had reported as a responder to the treatment while 47% of those who travelled to Colorado specifically for the drug testified to being a responder. The authors attribute this discrepancy in results to the idea that individuals willing to relocate or make great strides for the hope of a better treatment option are likely to have a strong desire for the drug to work, inherently creating a potential bias. Similar questions and concerns could be said for this study, which was run as an open-label trial where every child received the drug as part of an expanded access trial. Many of the parents and guardians who entered their children into this study did so with limited to no other options left to help relieve the deficits and health problems caused by their child's intractable generalized epilepsy. Due to this susceptibility, the placebo effect as it relates to the parent reported data couldn't be diminished for our analysis. It is for this reason that clinically proven and utilized questionnaires, such as some of those used in this study, are extremely valuable for determining safety and efficacy of drug studies and especially those using a compound such as CBD, which generates just as many questions as it does answers and needs more sophisticated assessments to be used. To improve the significance of the results found in the study, a larger double-blind placebo-controlled clinical trial using the same drug would be valuable to mitigate a placebo effect.

The results of all behavioral valuations, including anecdotal changes presented by the parents, make it challenging to determine what exact areas of a child's well-being and quality of life are being improved, though they do give some insight into what future assessments should continue to focus on. The clinical assessments used in this study

paired well with most parent results, which showed improvements in behavior, alertness, sleep, communication, and overall quality of life, regardless of the improvement in seizure activity but certainly more so in those who had a better reduction the frequency of their seizures. While all children in the study were diagnosed with intractable generalized epilepsy, their symptoms, deficits, and lifestyle all varied in many ways. Other factors such as currently used AEDs and their own side effects, as well as race, age, sex, socioeconomic status, etc. were not considered when analyzing the assessments used in this study, and all or many more could greatly affect the outcome of their results. We support the need for more studies to examine the specific changes in some of the participant improvements found in this study, such as attention, behavior, and sleep. Studying these changes, while also controlling for the other patient-specific factors mentioned, will help to draw more concise conclusions of the effect CBD has on the behavior, function, and quality of life of children with intractable generalized epilepsy.

CHAPTER 5
EFFECT OF CANNABIDIOL ON EEG AND EPILEPTIFORM DISCHARGES

EEG Methods and Study Design

Electroencephalography (EEG) is a common clinical test that is used to detect variations or unexpected electrical activity within the brain by tracking patterns in brain waves. It is estimated that almost every patient who has epilepsy or has shown epileptic-like symptoms has had an EEG recording performed. These tests can be extremely useful in evaluating abnormal activity, diagnosis or indication of a specific disorder, or the location of seizure activity. It is with using EEG recordings that most physicians are able to detect and diagnose intractable generalized epilepsy where generalized background slowing and abnormal activity throughout the brain is often seen. EEG's are extremely useful as a measure of physiological changes due to their being both a standard of medical care and having high test-retest reliability. They are a reliable and sensitive measure of cerebral function and have shown to be reactive to AEDs acting on the central nervous system. The goal of this analysis was to determine if cannabidiol has an effect on the EEG of children participating in this study and to explore the potential correlation between the effects we have seen CBD have on physical seizures and behavior to the recorded epileptiform discharges and activity found in the brain. An improvement in mood and attention has been reported in this present study, which parents and guardians have associated with the use of CBD. For this reason we aim to determine if there is a corresponding relationship to the spike-wave episodes found in the EEGs of these children, as this would be the corresponding measure to the anecdotal reports. Ideally we will be able to use seizure frequency captured by the EEGs as a biomarker of CBD treatment response.

From the participants enrolled in this open-label study, ten (n = 10) were randomly selected and had EEG's performed within one to three months before CBD treatment and then again one to two months after the 6-month trial period had concluded. The EEG analysis was longitudinal and each of the participants acted as their own control. The mean age of the participants was 11.5 years and included 7 males and 3 females, all at a maximum dosage of 25 mg/kg/day and a mean of 2.9 other AEDs at the end of the study. EEG recording was performed for a 24-hour period for all participants and took place in the Pediatric Departments at the University of Florida Shands Hospital in Gainesville, Florida and Duke University Hospital in Durham, North Carolina. Patients were kept in their beds in a lying position and instructed not to leave albeit to use the restroom. Standard gel-filled cup electrodes were placed using collodion at the frontopolar (Fp1, Fp2), dorsolateral prefrontal (F3, F4), central (C3, C4), and inferior lateral (F7, F8) locations of the international 10-20 system, with Cz as the common reference. All EEG signals were sampled at a rate of 256 Hz with a frequency response between 0.05 and 70 Hz.

As a preliminary exploration, a neurologist with expertise and experience reading the EEG's of children with epilepsy was asked to perform an evaluation of each child's EEG at baseline and then again after 6-months of CBD treatment without prior knowledge of the clinical results. The physician was asked to describe any background noise, epileptiform discharges, and changes in rhythm (Table 5-1). The baseline reading also confirmed generalized epileptiform activity for each of the ten participants, ensuring comparable results for the selected group. All ten recordings were inspected for artifacts likely caused by the child's movements, eye blinking, or loosening of electrodes, which

were then removed from the dataset. To analyze the remaining digitized EEG data, the epileptiform discharges were quantified by visual examination, which included any spike and sharp waves, polyspikes, and spike and wave complexes. Single epileptiform discharges were counted separately and any discharges that occurred for longer periods with multiple epileptic events were also counted and the total duration of the period was logged. An automatic detection feature was used to estimate the number of single spike discharges at each electrode location.

Table 5-1. Physician EEG reading notes.

Patient No.	Seizure Reduction (%)	Baseline Reading Notes	6-Month Reading Notes
1	88	Slow disorganized background. Generalized slow spike wave.	Slow background, more organized. Spikes are less in frequency.
2	12	Slow disorganized background. Frequent bi-frontal discharges.	No change.
3	54	Slow disorganized background. Generalized slow spike wave.	Slightly faster background. Less discharges and more reactive.
4	98	Slow disorganized background. No dominate rhythm.	Almost normal with dominant rhythm. No discharges.
5	96	Left frontal spike wave. Multifocal spikes.	More organized, faster, less spike waves.
6	100	Slow and diffuse background. No dominate rhythm.	More organized background. Few discharges.
7	52	Slow disorganized background. Generalized slow spike wave.	No change.
8	40	Slow disorganized background. Generalized slow spike wave.	More organized, faster background. Multiple events.
9	81	Right frontal spike wave discharge.	Faster and more organized. Still some events.
10	30	Slow background. Dominate frontal discharge.	No change in background. More spike wave discharge on right side.

Epilepsy and the use of some currently available AEDs have shown to be a possible cause of slowing in the background of EEGs, which in turn can be correlated to cognitive deficits. Increased theta and delta in conjunction with a decreased alpha frequency is commonly reflected in the EEG of these patients. For this reason we also analyzed the background EEG frequency and the peak frequencies within the alpha band. At the beginning of each 24-hour session, a period of 15 to 20 minutes of eyes closed monitoring was performed. Signals from this time period were collected and then broken into 4-second epochs. Each epoch was edited to remove any abnormalities or artifacts, leaving approximately 30 to 35 epochs. Performing the spectral analysis involved use of the Fast Fourier Transform at each electrode with a sampling rate of 128 times/s. To further process the data the relative power in the theta, delta, and alpha frequency bands were calculated.[84] The spectral analysis was performed for each frequency band of delta (0.5-3.5 Hz), theta (4 to 7.5 Hz), and alpha (8 to 12.5 Hz). Powers were normalized using the equation[85]:

$$log\left(\frac{x}{1-x}\right); x = relative\ power$$

It is important to not only assess the effect of CBD on the number of epileptiform events, but to determine if this new treatment has a positive or detrimental effect on EEG background frequencies and cognitive functions as a related result. An automatic recognition program was used to detect and quantify temporal and spatial distribution of all epileptiform events for the entire data-recording period. All data from the 9 electrodes underwent an analysis of variance (ANOVA, one-way) using their averages. Statistical analysis was performed on the number of discharges using the Wilcoxon signed-rank test. A $p < 0.05$ was considered statistically significant.

Results of EEG Recordings

Figure 5-1 illustrates the distribution of single epileptic spikes in five (n = 5) patients before and after the 6-months of CBD treatment. They were selected to represent a range of seizure frequency response from a 12% reduction to 98%.

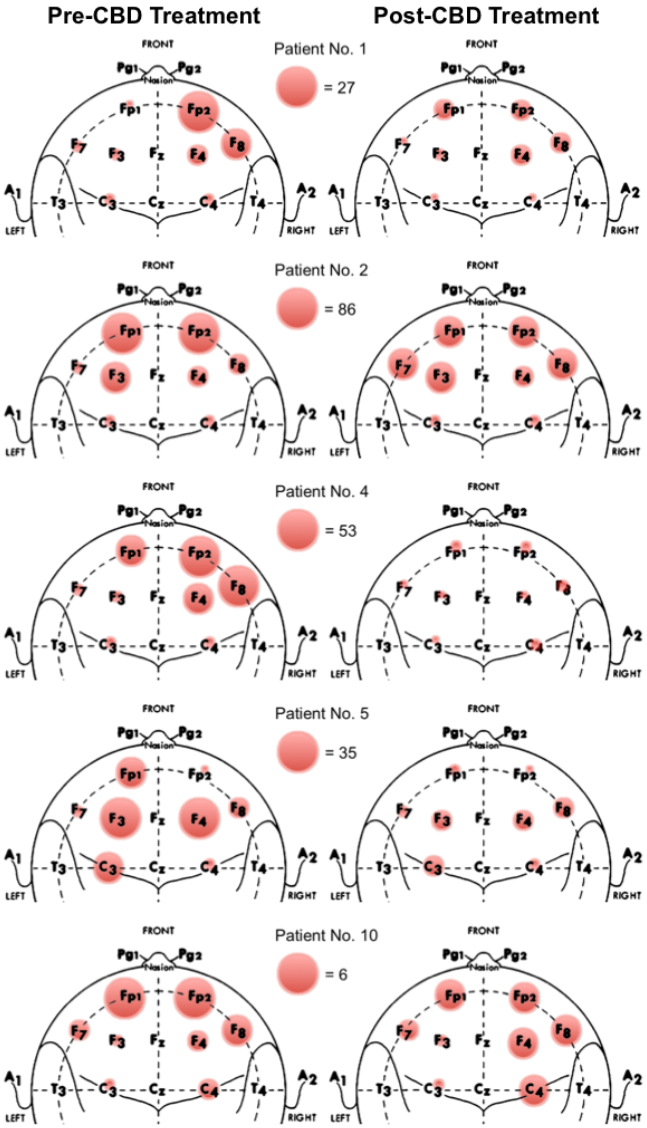

Figure 5-1. Distribution of single spike discharges before and after CBD treatment.

The figure demonstrates under which areas of the brain each of the single discharges most commonly occurred. We see that after CBD treatment the generalized discharges were either reduced or more evenly distributed throughout the front of the

brain. The total number of single epileptic discharges and the total time of discharges occurring in over periods were quantified for each individual patient and are shown in Table 5-2.

All ten participants who had completed EEG's both at baseline and 6 months after CBD treatment had a reduction in seizure frequency based upon the parent-completed seizure diaries, with seven of the ten being considered responders (>50% reduction). All parents or guardians, as well as the study physicians, reported either minor or significant improvements in the overall behavior of the ten patients. There was found to be a great deal of variation between each participant in regards to both single discharges and the total duration of epileptic incidents.

Table 5-2. Single and periods of epileptic discharges after 6-Months of CBD treatment.

Patient No.	Seizure Frequency Reduction (%)	Single Discharges (Number)			Periods of Discharges (Seconds)		
		Baseline	6 Months	Change (%)	Baseline	6 Months	Change (%)
1	-88	68	13	-63.2	19	2	-89.5
2	-12	345	359	+4.1	265	189	-28.7
3	-54	246	178	-27.6	107	34	-68.2
4	-98	215	16	-92.6	342	0	-100.0
5	-96	131	54	-58.8	216	46	-78.7
6	-100	88	33	-62.5	41	0	-100.0
7	-52	581	493	-15.2	327	8	-97.6
8	-40	46	38	-17.4	93	21	-77.4
9	-81	112	39	-65.2	252	18	-92.9
10	-30	24	26	+8.3	15	7	-53.3

When compared to the number of single discharges recorded during the 24-hour EEG, five (n = 5) participants had a >50% reduction after 6 months of treatment and two (n = 2) had an increase. The two participants who had an increase in single discharges in the EEG also had a clinical response of <50% in seizure frequency. The mean reduction of single spikes and sharp waves over the 6 month trial period was -39.0%.

Nine (n = 9) of the ten participants had a response >50% in total duration of periods of discharges, with a mean reduction of -78.6% of repetitive epileptic events. Two (n = 2) participants were complete free of periods of epileptic discharge and none saw an increase in total duration. These results show a statistically significant ($p < 0.05$) variation in the total number of periods of epileptiform discharges over time with CBD treatment between each patient. While there was a great deal of disparity from participant to participant in regards to the number of incidents recorded in the one 24-hour EEG, the number of single discharges and period of discharge show that there is some trend towards a reduction in the mean seizure frequency after use of CBD for 6 months.

To better understand the reduction seen in the periods of epileptic discharge, further investigation was performed where the periods were broken into three durations from 0 to 10, 10 to 30, and those greater than 30 seconds. The mean number and the mean duration were calculated for each of the time groups (Table 5-3).

Table 5-3. Mean number and duration of periods of discharges after 6-months of CBD treatment.

Period Group (Sec)		Baseline	6 Months	Change (%)	p
0 to 10	Number	213	134	-37.1	0.19
	Duration	712	458	-35.7	0.21
10 to 30	Number	33	28	-15.2	0.18
	Duration	495	428	-13.5	0.23
>30	Number	3	0.1	-96.7	0.02
	Duration	104	5	-95.2	0.04

Of the three time groups, those periods that were >30 seconds had the most significant reduction in both mean number and duration of -96.7% and -95.2%, respectively ($p < 0.05$). Both groups between 0 and 30 seconds did not see statistically

significant changes in either the mean number or duration of periods, with a decrease still shown in both ($p > 0.05$). Of the two groups, the shorter periods between 0 and 10 seconds decreased more than two-times that of those between 10 and 30 seconds in both number and total duration.

These results are comparable to a study using similar methods of both EEG and analysis of periods of epileptic discharges, where the drug Lamotrigine (LTG) decreased the mean duration of all periods by 81% and had the most significant effect on periods >30 seconds.[86] The twelve patients in that study were between the ages of 4 and 21 and had also been diagnosed with generalized drug-resistant epilepsy. Nine of the thirty participants completing this study were also using LTG as a concurrent AED, with no notable seizure control resulting. The spectral data for the three bands of background activity were compared between baseline and after 6 months of the added treatment of CBD, shown in Table 5-4. There was a decrease in delta relative power after treatment from 21.6% to 18.7%. Theta showed a similar movement, decreasing more significantly from 39.6% to 32.3%, and the alpha relative power increased from 14.9% to 21.1%. The statistical analysis performed on the data showed no significant changes amongst these three bands, though a marked trend of improvement can be seen from the calculated increases and decreases.

Table 5-4. EEG background activity changes after 6 months of CBD treatment

Frequency Band	Baseline Mean Relative Power (%)	6-Month Mean Relative Power (%)	Change (%)	Standard Deviation
Delta	21.6	18.7	-2.9	5.4
Theta	39.6	32.3	-7.3	8.8
Alpha	14.9	21.1	+6.2	5.6

Discussion of EEG Results.

The seizure frequency results of the ten children analyzed for the EEG portion of this study had a mean reduction of 71% after completion of 6 months of CBD treatment in conjunction with the patients other prescribed AEDs. Parents and guardians reported that their children had better moods and were more alert on CBD treatment, regardless of their individual seizure frequency or severity changes. A similar result was described in a retrospective review of children who had been given oral cannabis extracts (Press 2015). The improvements in frequency and behavior could be related, with the reduction of seizure activity and epileptic discharges intrinsically resulting in children becoming more alert and having improved concentration. It can be assumed that a reduction in periods of activity in children with intractable generalized epilepsy would prevent disruption in cognition and function. To assist in determining if the observed reduction of seizure activity and changes in behavior are related to periods of epileptic activity, the EEG's of the ten patients were completed and evaluated before and after treatment.

Five of the 10 participants had both a >50% reduction in seizure frequency as reported by the parents or guardians in the monthly seizure diaries as well as a >50% reduction in single epileptiform discharges from the EEG recordings. Of the remaining five who had <50% reduction in seizure frequency, three still had a reduction in single discharges (ranging from 15.2 to 27.6%) with two having an increase in the 6-month EEG recordings after CBD was introduced. A number of the patients still had higher than normal EEG peak recording after CBD treatment. Here we see there is some disparity in the results reported by parents or guardians and those shown in the EEG recordings. There are a few possible explanations of this difference. As noted in

previous chapters, the placebo effect cannot be ignored and it is possible that parents are not reporting all seizure events if they cannot properly identify them due to changes in activity they have never seen before in their child. Another more likely possibility is that the CBD has done well to reduce a majority of all physical seizures that can be easily recognized by parents or guardians while actually only reducing a fraction of those only identified by the EEG recordings. To better compare, the median percent reduction of single spike discharges was calculated to be a -32.7% from baseline, which is significantly lower than that of the parent reported results of -65.7%. Of the periods of epileptiform discharges, those that lasted for durations greater than 30 seconds saw the most significant decrease after CBD treatment. While a majority of the quantified single and periods of epileptiform discharges were not considered statistically significant, with the exception of the >30 second periods of discharge, the results of this study do show an important trend of reduction in activity after CBD use for 6 months. This decrease in both single events as well as the periods of epileptiform discharges does match that trend of seizure frequency reduction, with less activity persisting longer than 30 seconds, which would correspond to a possible improvement in alertness and cognition.

The spatial distribution of the single spike discharges showed an effective reduction in those who were considered responders, which pairs well with the reported decrease in seizure frequency and measured discharges. A distribution of any remaining discharges throughout the brain was shown for most participants after CBD treatment, with areas of high concentration being diverted to other areas. Slowing of EEG background activity is very common in children with epilepsy and is often times attributed to the side effects and neurotoxicity of many AEDs.[84] The slowing of EEG

background often corresponds to physiological brain dysfunction, which was reported by the study team during clinical visits and noted by the physician who read the EEG results prior to quantitative analysis. The spectral analysis of the EEG background bands showed a decrease in delta and theta and an increase in in the alpha band, which would allude to an improvement in background activity for these children receiving CBD. This would again correspond to the improvement in behavior and seizure frequency seen in this study, while it is still noted that the data is not statistically significant to draw concise conclusions. A larger dataset including placebo-controls would greatly assist in further investigating this possible relationship.

We believed that the recorded improvements in overall seizure frequency, behavior, and parent-reported-alertness for the children taking CBD would correspond to improvements in EEG recorded epileptiform discharges and a decrease in background slowing. The intent was to be able to use seizure frequency shown in EEGs as a biomarker for the response shown by CBD treatment. With EEG recordings being considered a standard of care for nearly all patients with epilepsy, it could be a valuable and cost effective tool for assessing the use of CBD for certain patients. Due to the variation in reported results with that shown by the ten EEGs evaluated in this study, it is not appropriate to yet make this conclusion. The results do nothing to sway the hypothesis that this biomarker could still be used, however, and a randomized trial with a larger cohort of patients could make these improvements and this connection clearer. A study using the same open-label cannabidiol drug also began to evaluate the background frequency, focal slowing, reactivity, frequency of discharges, and total number of seizures in thirty (n = 30) EEGs of children and adults.[87] The results after one

month of CBD treatment appeared to show no effect on standard EEG parameters, though they believe their conclusion to be limited as it was only after a very short period of CBD use, most of which was titration. From these results we can determine that there is some effect of CBD treatment on single events and periods epileptiform discharges, as well as background activity with an overall trend towards improvement. There was no significant regression ore negative increase activity that would cause a physician alarm or that could be attributed to CBS use. It will be important for clinical trials to further assess the observed correlation between seizure frequency, EEG background activity, and behavioral measures. This study shows that CBD treatment is well tolerated by children with intractable generalized epilepsy and could provide beneficial changes to activity recorded during EEG.

CHAPTER 6
SAFETY MEASURES AND PHARMACOKINETIC INTERACTIONS BETWEEN CBD AND OTHER ANTIEPILEPTIC DRUGS

Safety Data Collection and AED Measures

To monitor the child's safety and insure that all organs and systems are continuing to functional normally, assess any risks, and perform maintenance on other medication while treatment with CBD was ongoing, standard blood tests were performed. At baseline and then every clinical visit to follow, blood was collected from all thirty-three participants and labs completed for chemistry, hematology, and concentrations of antiepileptic drugs. Any abnormal results, such as low or high concentrations outside the standardized normal range, were flagged by lab technicians and reviewed by the study's assigned physician to make any treatment decisions if necessary. A comparison of the mean blood chemistry results at baseline and 6 months were reported in the results to determine any long-term effects of CBD on these measures.

Any ongoing side effect events experienced by children as a result of their seizure activity or ongoing AED treatment were reported by parents or guardians at baseline before CBD was introduced and then noted with any adverse events throughout the length of the study. During the first month of CBD treatment, while the drug was being up titrated, parents or guardians were contacted via phone or email weekly to perform safety evaluations and monitor any possible side effects. After this first month, the study-associated physician determined if continued CBD use was safe for each individual participant, after which the safety evaluations were performed at each clinical visit. All patients continued to receive their other medications, maintained at a steady rate from one month before receiving CBD through the first three months of

treatment. Plasma levels of other AEDs were analyzed at each visit and kept constant by adjusting doses to meet their intended therapy use throughout the study. After 3 months of CBD use, and if the participant was at a steady dosage, other AEDs could be reduced if their own neurologist or acting physician felt appropriate to do so.

Most participants entering the study were on multiple AEDs at the start of the study; four receiving five AEDs, 6 were receiving 4 AEDs, 11 receiving 3 AEDs, 7 receiving 2 AEDs, and 5 receiving one AED, with an average of 2.8 being used across the entire cohort. As noted in earlier chapters, while it is highly unlikely that seizure control will occur after a failed attempt of more than one AED, many physicians still commonly prescribe a polytherapy regimen in an attempt to manage the child's seizure activity. A polytherapy can be problematic, where the multiple drug to drug interactions increases the likelihood of side effects such as a loss of cognition, rapid changes in mood, and a negative impact on behavior. AEDs are not meant to act as a preventative or as a cure, but are meant to assist in suppressing seizure activity and controlling any symptoms, but some AEDs are even known to increase seizure activity and elicit new seizure types.[88] With participants given the option to lower the dosages of their other AEDs 3 months after CBD was added, the study team also evaluated the effects of reducing the number of AEDs or dosages and documented any changes in seizure frequency, behavior, or side effects as a result of doing so in the months to follow.

While the drug-to-drug interactions of CBD are not completely known or understood, a similar study investigated the related side effects and metabolized levels of the common AED clobazam (CLB) in patients with childhood refractory epilepsy who were taking CBD (Epidiolex) as a possible treatment.[58] It was found that CLB levels

were elevated after CBD was introduced, as were related side effects. Seizure reduction continued and the resulting side effects were alleviated once CLB dosages were reduced. The study members concluded that CBD was both safe and effective as a treatment option, but that it is also likely metabolized in the same pathway as CLB, requiring clinicians to more carefully monitor its use concomitantly with CLB. The results of this study led us to continue this research and examine the effect CBD had on all forms of benzodiazepine AEDs taken by the children in this study, including CLB, diazepam (DZP), and clonazepam (CLN). While the participants in this study were using a combined total of twelve AEDs, the most commonly used were the three benzodiazepines, with 13 patients were receiving CLB, 10 receiving clonazepam, and 16 using diazepam. These AEDs were also important to more closely evaluate due to their reported side effects with CBD[58] and likely similar mechanism method to that of CBD, inhibiting the GABA neurotransmitters[34].

The plasma levels of CBD, CLB, and CLN were analyzed at baseline, 3 months after CBD was introduced, and at the 6-month conclusion of the trial period. The percent increases in plasma levels were then analyzed by calculating the mean and standard deviations for all individuals taking each of the three medications. Diazepam is considered a ‘rescue medication’ used by all participants ‘as needed’ to stop cluster seizures or seizures that last longer and are unpredictable. Due to this inconsistent use of DZP compared to the other AEDs used by the children in this study, the number of times the rescue medication was administered the previous month was recorded at baseline, at 3 months, and at 6 months to assess the effect of CBD on the need for rescue medication by patients. CBD was maintained at a constant 25 mg/kg/day and

CLB, DZP, and CLN were adjusted as needed based on reported side effects and need to maintain consistent plasma levels. As with all other AEDs, participants were given the option to completely stop using these medications if the present study's assigned epileptologist, the parents or guardians, and their personal physician felt it was appropriate and safe to do so.

The primary outcome measure of all tests in this section was to assess the safety of introducing CBD as a treatment for children with intractable generalized epilepsy based on any changes in side effects, blood chemistry, as well as reported Adverse Events related to the drug. Secondary outcome measures related to the changes in seizure activity and side effects as AEDs were reduced after 3-months of seizure activity. Those who chose to reduce AEDs were analyzed both within the entire cohort of patients and then separately. We hypothesized that the study drug would be safe for participants to add as a treatment to their other existing drug regimens, and would have limited side effects comparable to previous studies using the same drug, Epidiolex. The results are all calculated as means and each group was compared by analysis of variance. The Wilcoxon signed rank test was used for analysis with a level of significance for all statistical tests being $p < 0.05$. All blood work was collected and had biochemistry and plasma levels analyzed by medical staff members in the University of Florida Clinical and Translational Science Institute laboratories.

Safety and Pharmacokinetic Results

The mean blood chemistry values at baseline (n = 33) and after 6 months of CBD treatment (n = 30) are shown in Table 6-1. These are considered the standard biochemistry values monitored during any drug trial for any abnormal changes and include the most common electrolytes and hematology. These chemistry screens help

tell the study team more about the child's general health and assess a treatments safety, and in this study we specifically evaluate the effect of CBD. The University of Florida Health Medical Lab normal pediatric ranges for each measure are provided in the table. Each patient has their blood chemistry analyzed by the UF Health Medical Lab and any abnormal values were flagged and then reviewed by the study physician. No patients in this study had any exceedingly high or low chemistry values that could be attributed to CBD use. Here we provide the blood chemistry results after long-term CBD use. We see that the means at both baseline and after 6 months are all within the normal ranges, with minimal changes over time.

Table 6-1. Blood Chemistry at baseline and 6-months after CBD treatment.

Biochemistry	Units	Normal Range	Mean at Baseline	Mean at 3-months	Mean at 6-months	Change (%) after 6-months
Sodium	mmol/l	136 - 145	140.4	138.6	139.9	-0.4
Potassium	mmol/l	3.3 – 5.1	4.0	3.9	3.9	-2.5
Chloride	mmol/l	98 – 107	101.7	103.1	101.0	-0.7
Creatinine	mg/dl	0.4 – 1.1	0.66	0.78	0.68	+2.1
Glucose	mg/dl	60 – 105	89.9	74.6	76.8	-14.5
Albumin	mg/L	0.5 – 19	6.1	6.0	5.8	-4.8
AST	U/L	0 – 41	32.5	29.3	29.5	-9.3
ALT	U/L	0 – 37	29.3	28.7	26.8	-8.5
WBC	K/ul	4.0 – 10.5	8.9	6.9	8.8	-1.1
RBC	K/ul	4.1 – 5.3	4.7	4.5	4.8	+2.1
Hematocrit	%	35 – 47	44.6	44.6	42.5	-4.7
Hemoglobin	g/dl	12 – 15	13.7	13.2	13.9	+1.5
MCV	FL	78 – 95	94.5	87.2	90.1	-4.7

The one value that was altered most significantly was Glucose, which had a 14.5% mean reduction in the entire cohort after CBD was introduced for 6 months compared to those collected at baseline. With such a high decrease, an initial concern raised by the study team was the possibility of continued glucose reduction to levels outside of the normal or safe range after the 6-month trial period. To clarify this, the blood work performed after 3 months of CBD treatment was utilized and the mean

glucose levels calculated. It was found that after 3 months of CBD treatment the mean glucose levels for the entire cohort of patients was 74.6 mg/dl, which is a 17.0% decrease. Here we note that while there is still a reduction worth monitoring, the glucose levels are stabilizing after an initial decrease.

Adverse events and side effects were reported by parents or guardians to be studied by team members at each clinical visit. Events that were reported throughout the study are shown in Table 6-2. These results include the thirty (n = 30) children who completed the the 6-month trial period. We see that drowsiness and lethargy were easily the most common side effects reported, with 56.7% and 36.7% of the cohort reporting incidents, respectively. For three of the participants who reported lethargy, the adverse event was affecting daily functioning negatively enough that it required their CBD dosage to be reduced from 25 mg/kg/day to 20 mg/kg/day as well as a reduction of other AEDs. After these adjustments were made normal function returned and the participants continued to tolerate CBD well throughout the period of analysis.

Table 6-2. Adverse events reported throughout CBD Treatment.

Adverse Event or Side Effect	Number of Incidents	Percent of Cohort Reported (%)
Drowsiness	17	56.7
Lethargy	11	36.7
Diarrhea	9	30.0
Weight Loss	5	16.7
Loss of Appetite	3	10.0
Constipation	3	10.0
Ataxia	2	6.7
Mood Swings	2	6.7
Hair Loss	1	3.3
Abnormal Gait	1	3.3
Irritability	1	3.3

Diarrhea was the third most common side effect reported (30.0%), much of which was attributed to the CBD being administered using sesame seed oil as a vehicle.

Sesame seed oil has been linked to digestive side effects including nausea, diarrhea, and stomach pain. While it does not directly represent an allergic reaction, the similar side effects seen by some participants in this study could be related to the copious amounts of oil digested in conjunction with the bonded CBD compound.

At baseline the mean number of AEDs being used by the children in the study was 2.8 (n = 33). All participants were expected to maintain a consistent dosage for the first three months of CBD treatment, unless it was medically required for health and safety purposes. After this initial period of consistent dosing, study participants were given the option to alter any of their other AED dosages. Table 6-3 shows the changes in usage for all 12 AEDs being administered in conjunction with CBD in this study. Six months after CBD treatment was introduced, the mean number of AEDs used by those completing the study was 2.1 (n = 30). Each AED being administered to the participants in this study was reduced, with Klonopin and Trileptal being completely stopped by the five patients receiving them at the start of the study.

Table 6-3. Change in AED use during CBD Treatment.

AED	Number of Patients Using	Number Using After 6 Months
Lamotrigine	9	5
Phenobarbital	6	5
Topomax	6	5
Clobazam	13	6
Keppra	8	5
Klonopin	1	0
Trileptal	4	0
Depakote	8	2
Banzel	5	1
Diazepam	16	4
Clonazepam	10	6
Valproic Acid	10	8

Not shown in the table but recorded and calculated by the study team was the mean number of times per month that Diazepam was used as a rescue medication for

severe seizure incidents. At baseline the 16 participants using DZP required its use a mean of 6.8 times (SD = 2.9) and then saw a significant reduction after CBD treatment was introduced where 4 of the initial 16 participants used the medication a mean of 1.2 times (SD = 1.4). The other 12 participants did not require use of DZP at the end of the 6-month trial period. This decrease in DZP use parallels that of other AEDs that are administered as a daily dosage rather than 'as needed'.

Changes in adverse events and side effects were recorded from what was experienced at baseline and then after completion of the study for the twenty-seven (n = 27) children receiving CBD treatment for the 6-month trial period who also reduced or stopped taking other AEDs (Table 6-4). The intent was to see if there were any notable fluctuations in side effects with both the addition of CBD as a treatment and the reduction of medications that have been shown to cause adverse events. There were no statistically significant changes in events ($p > 0.05$) due to the small sample size, though there was a notable trend towards a reduction in the number of incidents reported.

Table 6-4. Adverse events reported at baseline and after CBD treatment and reduction in AEDs.

Adverse Event or Side Effect	Number Reported at Baseline	Number Reported at 6-months	Change (%)
Drowsiness	20	11	-45.0
Mood Swings	17	6	-64.7
Lethargy	14	5	-64.3
Ataxia	14	5	-64.3
Constipation	9	3	-66.7
Irritability	9	1	-88.9
Obesity	6	4	-33.3
Weight Loss	5	2	-60.0
Loss of Appetite	5	0	-100.0

There was a mean percent reduction of 65.2% across all recorded events and no participants noted an increase in seizure activity after decreasing the use of their other

AEDs. Typically, there is an associated or expected increase in seizure frequency while the child adjusts to dosage changes, but no significant increase being seen by those in this study is a positive sign for control over their neuronal activity. Constipation, Irritability, and loss of appetite saw the greatest reduction in occurrences (-66.7%, -88.9%, and -100%, respectively).

The plasma concentrations analyzed with the collected blood samples did show there is a relationship and interaction between CLN, CLB, and CBD. Figure 6-1 displays the mean plasma concentrations of CLN (n = 10), CLB (n = 13), and CBD (n = 30) at baseline, 3 months after CBD was introduced, and then for 6 months after. The mean changes in plasma concentration of each drug was considered statistically significant ($p < 0.05$). At baseline the mean plasma concentrations were 0.232 ug/ml for CLN and 0.361 ug/ml for CLB, which are within expected therapeutic ranges[89]. After CBD was added to the participant's treatment regimen, the plasma concentrations increased considerably with CBD levels at 0.195 ug/ml, CLN levels barely within therapeutic range (0.1 to 0.6) at 0.579 ug/ml, and CLB exceeded therapeutic ranges (0.2 to 0.7) at 0.758 ug/ml. In every participant, the CLB and CLN levels were higher after 3 months of CBD treatment than at the start. From baseline this represents a 59.9% and 52.4% increase for CLN and CLB, respectively.

Of those participants taking one or more of the three drugs being related, drowsiness (n = 11), lethargy (n = 9), and ataxia (n = 2) were reported as significant adverse events. None reported an increase in seizure activity and many still reported a significant decrease. To regain appropriate plasma concentrations and to assist in alleviating the worsening side effects, CLN and CLB dosages were reduced or

eliminated. By the end of the study, 4 out of 10 participants stopped using CLN and 7 of 13 stopped use of CLB, with all other participants reducing dosages for both medications. After 6 months, the mean concentrations were back to within desired therapeutic ranges with CLN at 0.318 ug/ml (n = 6) and CLB at 0.486 ug/ml (n = 6). CBD increased to a statistically significant mean plasma concentration of 0.324 ug/ml (n = 30, $p < 0.05$). Here we observe that while dosages of CLN and CLB decreased, with some participants completely stopping treatment, the mean concentrations were still higher after 6 months of CBD use than at the start of the study.

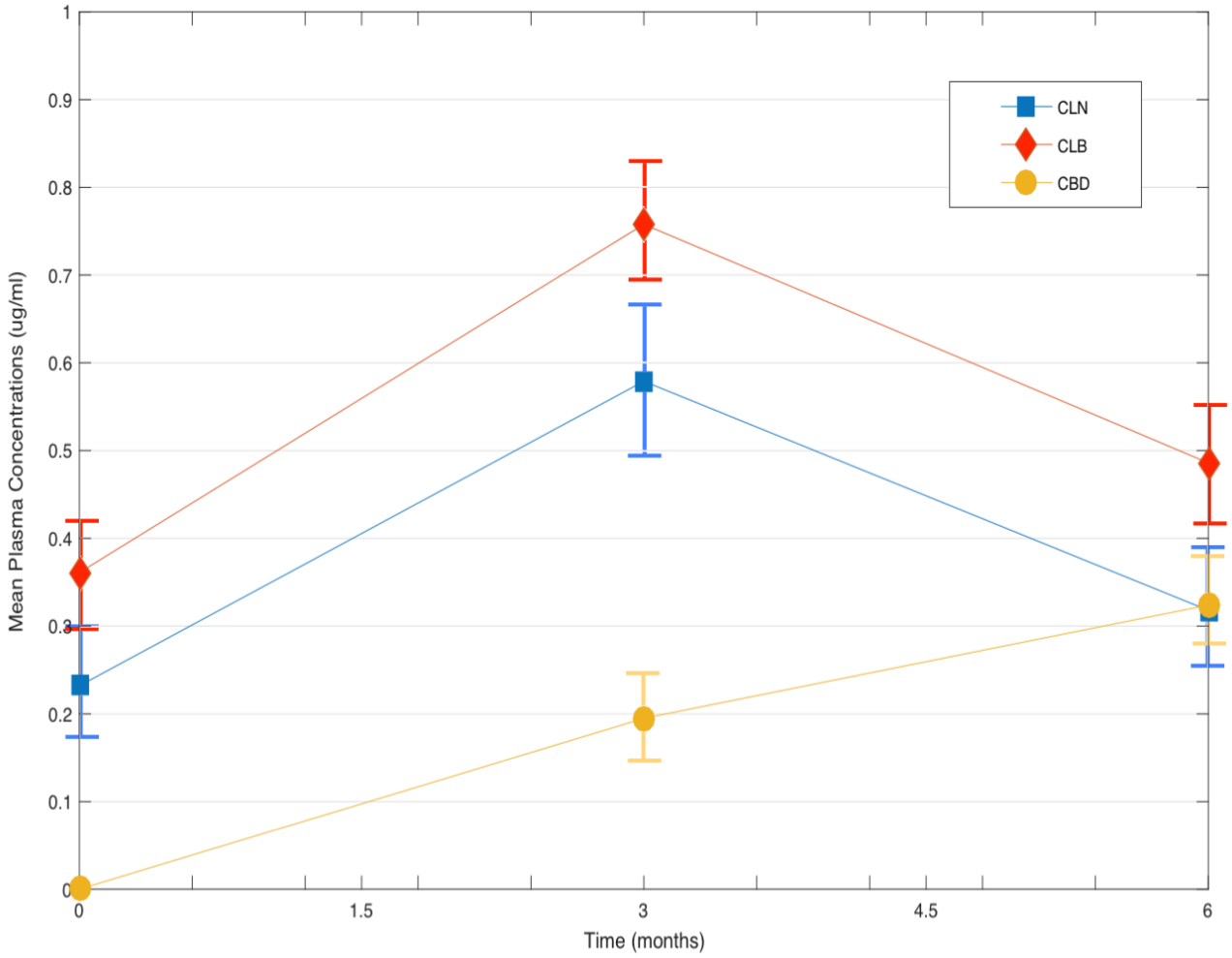

Figure 6-1. Mean plasma concentrations of CLN, CLB, and CBD at baseline, 3 months, and 6 months after CBD treatment was added.

Discussion of Safety and Pharmacokinetic Results.

The biochemistry results collected from the participant blood samples showed that CBD had very little effect on the electrolyte or hematology concentrations for the children enrolled in this study. All results remained within normal range and no individual incident of a high or low level could be attributed to CBD treatment. As noted, glucose did decrease a significant amount across all participants. While there is no direct relationship between glutamate/GABA release and glucose levels, the decrease could allude to the hypothesized inhibition of GABA neurotransmission by CBD as a mechanism of action. Glutamate is one of the primary neurotransmitters in the brain, and when in excess it can overstimulate neuronal pathways and cause seizure activity. High glutamate levels can cause a variety of disorders or debilitating neurological deficits, making the likely reduction and control from CBD an important attribute of the drug. It is common to see elevated levels of glucose in children with epilepsy, and the increase in synaptic activity creates a greater demand and, in turn, an increase in that produced by the body. Other FDA-approved AEDs, such as carbamazepine and Topamax, have also shown to result in a reduction in glucose after extensive use by children with epilepsy.[90] The reduction in glucose levels after CBD treatment would correspond to a reduction in neuronal activity as there is less of a need for a large supply to be generated and stored, creating more normal conditions.

Side effects were reported throughout the study in 75.8% of the participants, though only three (9.1%) discontinued CBD use. Most of the adverse events and side effects were considered so mild that the improvement in seizure activity and behavior easily outweighed those reported. The two side effects most reported by participants

were drowsiness and lethargy, which could also be related to the decreased glucose levels where blood sugar would cause a decrease in overall energy. These standard drug trial assessments show that CBD is safe, has limited side effects, and is well tolerated by children with intractable generalized epilepsy.

We also wanted to investigate the pharmacokinetic interactions between CBD and the other concomitant drugs being taken by the intractably epileptic children in this study. Most of the participants were on multiple AEDs at the time of baseline measures, as per recommendation of their personal neurologists. This is regardless evidence suggesting that polytherapy is not an effective treatment option for these children whose epilepsy is drug-resistant. The use of multiple AEDs often leads to an increase in side effects and sometimes a worsening of pre-existing seizure activity and cognitive deficits. It is well understood that AEDs can result in dose-related adverse events due to general dampening of neuronal activity in the central nervous system.[34] The mean number of AEDs used was reduced from 2.8 to 2.1 by all participants after 6 months of CBD treatment, with five receiving CBD as monotherapy treatment. Corresponding to the decrease in AED dosages was a decrease in adverse event incidents with either a continued reduction or no change in seizure frequency. One possible reason for the decrease in side effects from baseline could be because the pharmacokinetic drug interactions between the pre-existing AEDs as well as those with CBD were minimized from the dosage reductions. This would also explain the continued improvement in seizure frequency where better drug levels and reduction of other medications reduces the risk of seizure increases that some AEDs are reported to cause. The reduction in side effects shown by this present study after a reduction of other AEDs are comparable

to results reported by Dash et al. where 962 patients with drug-resistant epilepsy reduced their mean AED usage from 4.24 to 2.65 and 82.70% saw a decrease or no change in seizure activity and a significant improvement in adverse events reported after 6 months of tapering.[88] The reduction in rescue medication use is also significant to note, as these medications are often very harmful to the child and can cause a number of cognitive deficits after repeated use[91].

A drug-drug interaction between CBD, CLN, and CLB was also shown by an increase in mean plasma levels for both pre-existing AEDs. A worsening of side effects and the increased levels are likely due to CBD inhibiting the same neuronal pathways that metabolize both CLN and CLB, causing an accumulation of both drugs. Benzodiazepines, such as CLN and CLB, increase the frequency of chloride channel opening, activating GABA receptors and enhancing the synaptic GABA release. This inhibits neurotransmission in the central nervous system and causes a hyperpolarizing effect, resulting in decreased neuronal and seizure activity.[34] While CBD plasma levels do not appear to correlate to CLN or CLB levels, showing no effect of these AEDs on CBD metabolism, it is likely that they are all interacting through the same or similar mechanisms of action, supporting the results of other studies that the inhibition caused by CBD elevates benzodiazepine levels.[58] The accumulation of CLN and CLB could be attributed to CBD inhibiting the CYP2C19 receptors that metabolize these AEDs and prevent them from completely entering the central nervous system. While we see that this drug-to-drug interaction between CBD and the other benzodiazepines resulted in the number of reported events with lethargy and drowsiness, a decrease in these other AEDs reduced all related side effects and CBD caused no seriously negative effects in

conjunction. Physicians prescribing CBD in the future will need to understand these interactions and control dosages of all medications appropriately.

Limitations to this section's analysis include the small sample size for all calculated means and the open-label nature of the study. For this reason, we strongly encourage more placebo-controlled and blinded studies to evaluate the safety, efficacy, and interactions that CBD has as a treatment option of pediatric intractable epilepsy and seizure activity. While a trend of improvement is shown, statistical significance needs to be achieved before direct conclusions can be made. Ideally we would want to compare groups of participants who were on the same regimen of AEDs, but the smaller population of children in this study had such varying use of AEDs that it was not appropriate to attempt a statistical comparison. A larger cohort of patients or added inclusion/exclusion criteria of certain AEDs will further assist in determining the drug-to-drug interaction CBD may have. We can see that it is ideal to reduce the number of AEDs given to children with intractable generalized epilepsy, with better seizure control and adverse reactions because of this reduction.

The use of CBD has allowed for these participants to reduce their reliance on other AEDs and form better drug combinations for improved results. While this is ideal for the participants and their families, it is also important to note that after 3 months of CBD treatment the study participants were permitted have their other AEDs reduced or dropped completely. This very well could have had an effect on the results of both the drug-to drug interactions, effectiveness of CBD, measures used in this study, and the side effects reported over time. While more sophisticated studies need to be performed to better analyze the mechanism of action of CBD in the child's brain, we can conclude

that it is active in regulating the neuronal environment and assists in creating the important balance between excitation and inhibition in the central nervous system. The evidence shown in the present study reveals that CBD is safe and well tolerated by children with intractable generalized epilepsy and successfully replaces other AEDs or allow for a reduction in polytherapy treatment plans.

CHAPTER 7
STUDY CONCLUSIONS AND FUTURE DIRECTIONS OF RESEARCH

The use of cannabis or its byproducts for medicinal purposes is nothing revolutionary to field of medicine with many reports showing beneficial expenditures throughout history, including seizure management. While several political, racial, ethical, and socioeconomic decisions by previous lawmakers prevented the true medicinal potential of cannabis from being studied and discovered for many years, recent interest and excitement for the potential benefits that could be provided by the drug has opened an avenue for a new opportunity to explore its possible use for a number of conditions and ailments, including epilepsy. News reports, social media coverage, and several journal reviews have highlighted a significant amount of anecdotal evidence of the potential efficacy of cannabidiol for the treatment of seizure activity and related epilepsy symptoms. This increased public awareness of the potential of cannabidiol has lead to an influx of patients, caregivers, physicians, growers, and legislators to seek out legalization and limit the restrictions that are preventing necessary research from taking place. Several pharmaceutical companies have begun to take advantage of the progression of interest and demand, and they have started the development of their own CBD-based medications, including the one used in this study, Epidiolex (GW Pharmaceuticals). Recent open-label studies using these new drugs have shown that CBD can be both safe and effective in controlling seizure activity for both children and adults in epilepsy. There have been an increase in preclinical animal studies and clinical trials that have shown that CBD could be a safe and effective drug with comparable antiepileptic capabilities that are comparable to currently available and FDA approved AEDs.[58] What made this study unique was that we targeted a population of children with

intractable generalized epilepsy and examined, not only if CBD could help to safely improve their otherwise drug-resistant seizure frequency, but to also see if the child's cognition, behavior, daily function, and overall quality of life could also be effected after treatment was introduced.

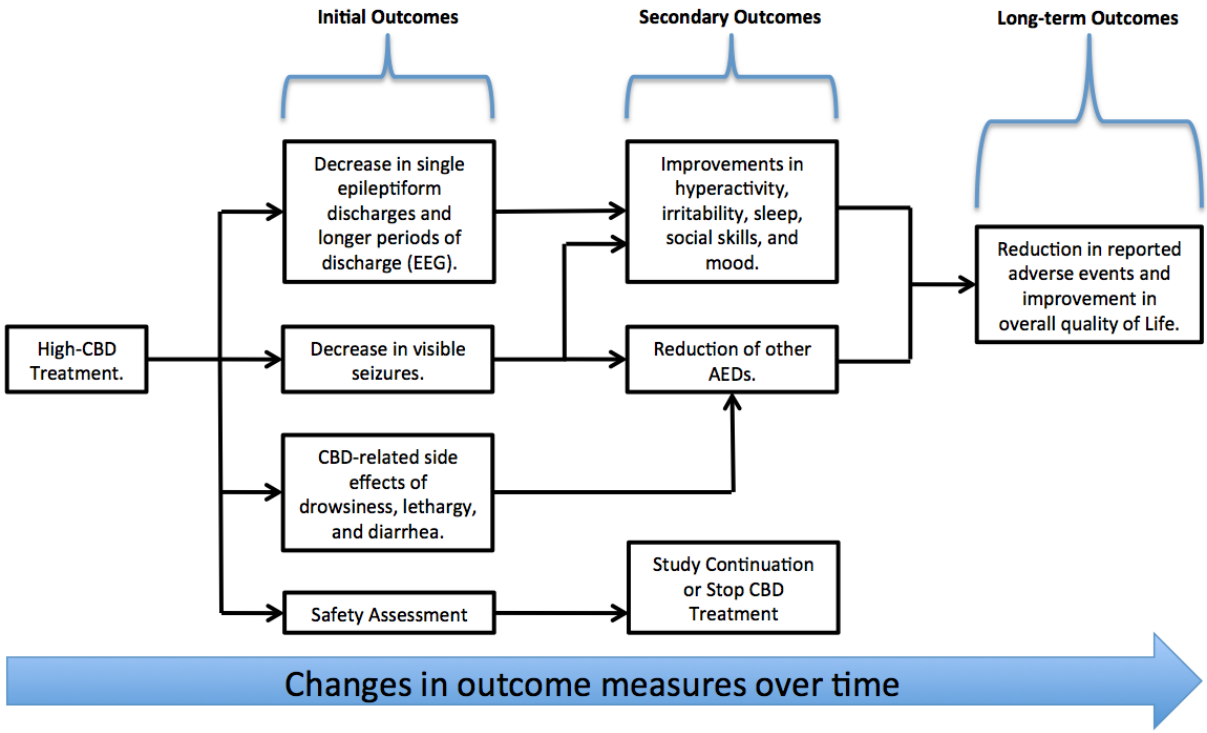

Figure 7-1. Effect of CBD treatment on the outcomes measured for each child with intractable generalized epilepsy.

Our original hypothesis was that CBD, when taken in high-concentration form by children with intractable generalized epilepsy, would not only safely improve seizure frequency but also improve daily and adaptive behavior and function. The results of this study show, or in the least, present strong evidence that CBD is able to have a positive effect on both measures from a concatenation of initially altering seizure activity which then leads to other changes in the child's behavior and an overall improvement I the quality of life (Figure 7-1). From the primary outcome measure of seizure frequency, we saw a significant reduction in the median parent-reported monthly seizures of 34.3% for

the thirty participants completing the study, with 70% of the cohort being considered responders to the CBD treatment. This is comparable to the results of the study performed by Devinsky et al.,[23] who used the same study drug across several sites, with this current study reporting a higher number of responders. To further add to the parent reported seizure results, the EEG analysis performed on ten study participants with varying monthly seizure reduction. The blinded-physician readings and measure of epileptic discharges in the EEGs revealed a corresponding reduction in single spike discharges and the longer periods of discharge, enforcing the reported seizure reduction results.

By the end of the 6-month treatment period, 30 of the 33 participants had completed the trial with minimal side effects and only a handful of adverse events reported that could be directly related to the introduction of CBD into their regimen, many of which were alleviated by altering the dosages of other AEDs. Biochemistry results collected from each child's blood work revealed no concerning levels outside of the established normal range, though it was noted that there was a significant decrease in glucose levels. While within a safe range and well monitored, this drop in blood sugar could have added to the reported lethargy and drowsiness that a significant number of participants experienced. The higher than expected incidence of diarrhea is likely related to the use of sesame seed oil as a vehicle for the drug rather than an interaction with the CBD, which could eventually be alleviated once other forms of administration are developed. Many of the side effects reported were considered tolerable by the patients or their guardians and did not negatively impact their day-to-day activities. Overall we see that CBD demonstrates effective reduction in epileptic seizure activity

and does so with fewer side effects than most FDA-approved and clinically administered AEDs. Though we reported the safety of CBD over the course of 6 months, it is also important for future studies to examine the efficacy or negative impact that long-term use of CBD may have on the developing brain of a child. For a physician to comfortably administer CBD as a long-term treatment option a dosage assessment should be performed to better understand the acute and enduring neurotoxicity associated with the drug. That said, the deficits many of the participants in this study experienced resulting from their intractable epilepsy were so debilitating, any relief that the CBD assisted in producing for each child's cognitive and functional development likely far outweighs the possible negative impact of long-term CBD use.

The changes in the participant's behavior and daily function that were recorded in this study do not reveal a direct response from the CBD treatment but rather a chain-reaction to the reduction in seizure frequency and epileptiform activity. The overall improvement in the children's irritability, hyperactivity, sleep duration, night waking, socialization, and even those anecdotally reported by parents such as memory, attention, and mood can all be linked to what an epileptologist would expect from a decrease in seizures and a reduction in epileptic activity. The decreases in the distribution of single spike discharges shown at the frontal electrode sites in the EEG recordings correspond to the improvements measured by the study questionnaires. These areas in the brain control function and behavior associated with emotional inhibition, social awareness, impulsivity, irritability, mood, and attention. Here we can determine that the seizure results pair well with the behavior data, where reducing activity can in turn improve function. There is a significant amount of anecdotal evidence

reported that claim that CBD can be used to solely treat disruptive behaviors and improve sleep, concentration, or social interactions in children with disabilities associated with epilepsy. While the focus of this study and many others is the central nervous system, cannabinoid receptors are found all throughout the brain and body, modulating many functions. For this reason, it is no surprise that scientists and physicians might expect cannabinoids such as CBD or THC to have a wide range of physiological effects and would do well to explain some of the therapeutic effects being anecdotally reported by individuals using these compounds as a form of self-treatment for numerous disabilities and health-related problems.

While more studies need to be performed to examine the specific areas of interest we have noted, this current study would allude to the circumstance that the improvements in these measures are a result of seizure frequency decreases and cannot be directly attributed to treatment with CBD. Participants who had a response of >50% in seizure reduction also showed a greater improvement in the behavior and daily function measures compared to those who had <50% reduction, further supporting our postulation of the downstream effect of CBD on the child's overall quality of life. Some of these improvements could also be attributed to the reduction in use of other antiepileptic drugs by a majority of the participants. As was previously discussed, long-term polytherapy using multiple AEDs is a common treatment method for most patients with intractable generalized epilepsy. The use of these AEDs together often results in many adverse events.[43] These incidents can be dosage related, with many patients needing higher-than-normal doses to gain any form of seizure control, hypersensitivity to the medication, negative drug-to-drug interactions, or even long-term side effects

after prolonged use of these powerful AEDs. Some of the adverse events are subtle while others are more apparent, but most are difficult to assess due to the natural deficits that these children with intractable epilepsy exhibit. While CBD was not without reported side effects, those that were observed were considered minimal and non-hindering to the child's daily function after the 6-month treatment period in comparison to the side effects caused by other AEDs.

For many patients and their parents or guardians, the risk of the side effects and adverse events attributed to CBD may be worth accepting since the risk of continued seizure activity can be considered to be far more detrimental to the overall health and safety of the child. By lowering or eliminating the use of other AEDs we believe we are also reducing the risk of adverse events that may be caused by polytherapy. This is especially true when discussing the use of rescue medications, such as diazepam, which was needed much less by participants in this study once they began receiving CBD. These rescue medications, while stopping severe seizure clusters, often carry their own risks to the child's wellbeing such as disruptions in breathing and loss of both behavior and motor function, making the ability to reduce their use even more valuable to these participants. When comparing the adverse events reported by participants at the baseline time point of this study, we saw less of those reported after 6 months of CBD treatment with many participants claiming improvements from before the drug was introduced into their daily regimen. Though some degree of this change could be directly correlated to seizure reduction, it is more likely a result of reducing their other AEDs resulting from better seizure control with the CBD treatment. For this reason, we would claim AED reduction as a secondary outcome of the use of CBD by these

patients. It cannot be ignored that reducing the reliance on other medications also reduces the economic impact on the families of these participants, due to the fact that many of these medications are considered to be quite costly.

It will be important for future studies to continue to assess the drug-to-drug interactions that CBD may have with other AEDs or medications commonly given to children with a similar diagnosis. While we found that the positive results of CBD on seizure activity resulted in a reduction in the use of other concomitant drugs, many participants opted to continue receiving the drugs, or decided to continue their use at lower doses as per recommendation of either their neurologist or their personal comfort with medication changes. In this study, as well as that performed by Geffrey et al.,[58] we observe that CBD has a clear interaction with benzodiazepines. The plasma levels not only increased for these AEDs after CBD was introduced, but a dramatic increase in lethargy and drowsiness was also noted by the patients taking these medications. All side effects were relieved after the benzodiazepine dosages were reduced or stopped completely. This interaction with other drugs needs to be considered in future studies where specific AEDs are targeted to determine the effect CBD may have on their effectiveness, concentrations, or related side effects. Doing so will help physicians and researchers both understand and how to appropriately administer CBD as a treatment and how to coordinate other concomitant medications around its delivery.

The interaction of CBD with the benzodiazepines also enforces the believed mechanism of action, where the drug inhibits metabolic enzymes including CYP2C19, which primarily metabolizes those particular AEDs.[92] This is likely the reason for an increase in concentrations of the benzodiazepines, as CBD is hindering their

metabolism into the central nervous system and causing toxic levels and the resulting side effects. The evidence would suggest that CBD could be increasing these levels and those of other cannabinoids due to this interference with metabolism and inhibiting the feedback process of neurons during periods of intense activity in the synapse. This inhibition assists in decreasing synaptic transmission during epileptiform activity and works to modulate receptors and their signaling, which would explain the reduction in seizure frequency and epileptic discharges as well as long-term psychological function changes in behavior, mood, and control over physical tasks. When looking at CBD as a possible treatment option, a physician will need to understand how the patient's seizures can be controlled and the probability of doing so based on the patient's medical and concomitant drug history.

It will be especially important in future study's to understand how CBD interacts with other antiepileptic drugs so that a neurologist can make educated decisions on how to appropriately prescribe CBD instead of other drugs or a combination of these medications together. While many patients with intractable generalized epilepsy will opt for the risks associated with combining these powerful drugs over the more severe gamble of doing nothing and allowing for the uncontrolled epilepsy and seizure activity to run its course, the possible mortality and morbidity associated with CBD used with other medications needs to be better understood. CBD's inhibition of the post-synaptic process increases the release of endocannabinoids, which then diffuse back and activate CB1 receptors and cause the inhibition other transmitters.[92] The entire feedback process is important when activity at the synapse is poorly controlled. This is a neurological progression that high-CBD alone, without the combination of other

cannabinoids to establish homeostasis, could over-inhibit and affect both efficacy and toxicity of the drug.

There is growing evidence that suggests endocannabinoids may work synergistically with each other to help modulate and balance the entire central nervous system, commonly referred to as the 'entourage effect'.[93] While this theory is mostly supported by medical marijuana enthusiasts who prefer a more 'natural' use of the drug to anything that is purified, the few animal studies available showing the benefits of THC, CBD, and other cannabinoids in combination is one that should be explored for human use. CBD's mechanisms of action provides this synergistic opportunity with cannabinoids and especially THC, where it can reduce the concerning psychoactive effects THC has on an individual. The animal data supports the 'entourage' effect, showing that CBD with THC may work well in combination as an anti-convulsant and may have an overall effect on both seizure control and symptoms of epilepsy. It is extremely difficult to properly test the synergistic effect in a controlled human study with most non-pharmaceutically produced cannabis preparations containing an inconsistent and wide variety of cannabinoids. This generates a study that is exceptionally susceptible to varying results and inconsistent data that would prove to not be clinically significant. An ideal drug trial for exploring this combined effect would include a handful of cannabis preparations with well-established, varying cannabinoid quantities, given to an epilepsy population blinded to the combination they are receiving. This would require a very large population and intricate study design, costing a great deal of time and money, but would be very useful and needed to further advance the research of cannabinoids, and one that could be performed after cannabis is more established in

modern day medicine. CBD in combination with other cannabinoids could prove to be a more beneficial treatment option for children with epilepsy, and a better understanding of this co-working effect may eventually lead to more effective patient-specific medication options.

This present study did well to unearth several additional questions regarding the safety and efficacy of CBD as a treatment option for intractable generalized epilepsy in children, though we were not without our challenges in regards to study design. While the data reported in this study provides valuable knowledge for CBD's use in this particular cohort of patients and will be able to springboard the development of other studies and forms of CBD-drugs, the open-label nature and low population of patients was obviously limiting to the results found outside of the primary outcome measures. Most of the data collected was from parent reported journals or questionnaires and, while the study team took all appropriate measures to insure consistency throughout the trial, the results are vulnerable to a placebo effect of parents wanting or expecting a certain outcome when they know their child is in fact receiving the study drug.

The diagnosis of the participants with intractable generalized epilepsy is an extremely broad approach, though necessary as many of these patients do not fit within many 'standard' epilepsy syndromes. A significant number of the participants in this study developed their epilepsy at different times in their lives and through varying genetics, medical catastrophes, or incidents, bringing up the question of efficacy for each specific abnormality. Trials involving AEDs or similar compounds are difficult to maintain control over due to the unpredictable occurrence of seizure activity as well as the varying types of seizures. It is for this reason we would highly suggest a placebo-

controlled, double-blind clinical trial using a significant number of patients, likely from multiple sites, who share very similar clinical backgrounds and epilepsy development. Importantly, clinical imaging studies are needed to establish the effects of CBD on structural and functional connectivity abnormalities that are now recognized to drive the behavioral features of ASD and other neural deficiencies.

Another insightful technique used in this study that avoids patient and parent/guardian placebo effect risk was the examination of patient EEG's. Observing several participants' EEG's in this study helped to determine if there was a corresponding change in epileptiform activity to that reported by parents and guardians throughout the course of the study. Future EEG studies could help to continue and solidify these results and determine if there are any connectivity changes after taking CBD over time. Longer, more extensive, EEG recording in a larger population of patients after the long-term use of CBD would be significant in determining if there is a measurable effect on overall brain connectivity. Pairing this with suitable behavioral tests and correlating any noted changes in electrical activity of different areas in the brain with functional outcomes would be a major step forward in better understanding the possible effects of CBD on the neuronal pathways of the brain. While this study provides sound preliminary data for this specific area of interest, a placebo-controlled study with more participants included would help to answer most of the remaining questions in regards to CBD's effect and mechanism of action.

The efficacy of CBD shown in this study on seizure control for these children who had been suffering with uncontrolled activity and related behavioral deficits helps to establish an opportunity for researchers to begin to look at other, similar childhood

disabilities that also impair quality of life. Drug resistant epilepsy is phenotypically heterogeneous with individuals expressing a range of conditions from mild-to-severe intellectual disabilities; sleep disturbances, mood disorders, and psychosis. Clinical evidence has shown that a significant percent of children will end up having co-morbid autism spectrum disorder (ASD). Because of the broad spectrum of behavioral symptoms in this population, it is often challenging to identify the effectiveness of new or available treatments. There is evidence in support of the use of CBD as a broad acting medication that might alleviate seizures while at the same time treat autistic behaviors, though the results we present in this study would conclude that the behavioral changes seen are likely a derivative of improved seizure control rather than directly caused by CBD interactions. That said, with such a substantial number anecdotal reports showing that CBD alleviates psychosis, anxiety, facilitates REM sleep, and suppresses hyperactivity, this promising range of therapeutic effects may benefit children with an ASD. To date, there are no clinical studies to determine the effects of CBD on only behavioral problems with face and construct validity.

As detailed, the high-CBD drug used in this study (Epidiolex) was taken orally by all participants and used sesame seed oil as an inactive vehicle of ingestion. Sesame seed oil is commonly used in many early-phase drug trials as it is generally well tolerated by many participants and works well to bind to the active compounds, especially soluble agents like cannabinoids. However, this type of oral delivery is not considered the most pharmacokinetically sound form of ingestion, because it has been estimated that the bioavailability of CBD is only 6% when administered in this manner, due to greater metabolism acting in the liver.[16] The most common form of delivery of

CBD and its constituents is inhalation via the smoke produced from igniting the cannabis plant. This is obviously an unsuitable method for medicinal use and especially not an appropriate routine for children, though the approach is valuable when searching for a more effective delivery method of CBD. It has been well established in medicine that the lungs are one of the best and most efficient pathways for delivering drugs into the human body. With this knowledge, some limited studies that have examined the bioavailability of CBD after aerosolization or vaporization, showing nearly 31% available in peak plasma concentrations. While those studies were performed within a small population and outside of clinical control, they do indicate the need for future studies and drug development using CBD to explore more effective delivery methods or devices for doing so to potentially improve the efficacy of the compound.

Children with intractable generalized epilepsy typically face many challenges that worsen their quality of life, create a host of social and behavioral problems, can force their families into a reduced socioeconomic lifestyle, and potentially increase their risk of death. These children and their families currently have no available options to alleviate the devastating toll that the uncontrolled seizures their children experience can have on them. It is for these reasons that there is a great need to find effective treatment options and explore the safety, efficacy and tolerability, of this promising drug, cannabidiol, for these desperate patients. While seizure reduction has a significant effect on the quality of life of the patient, looking at the other daily function changes that CBD could be causing in social behavior, cognition, or motor skills was also important. The results of this study showed that the introduction of high-CBD into their regular treatment regimen safely lead to significant reductions in their otherwise drug-resistant seizure frequency

and epileptiform activity. Over time we saw that this reduction in seizure activity led to improvements in the child's behavior, daily function, sleep, and overall quality of life. The reduction in seizure activity experienced by the child, also led to improvements in the quality of life of the entire family. Progress or generally positive changes in a patient's lifestyle are important in assessing how effective an AED, and especially CBD, can be. The evaluation of these changes examined in this study while participants were receiving CBD treatment is an important step in therapeutic testing of the drug.

Other clinical trials will need to look at the importance of dosage timing and the effectiveness of CBD in concurrence with other currently prescribed AED's, as well as any health risks that could be associated with taking these medications together. Examining how CBD combined with THC or other cannabinoids may work together, how the drug is administered, and at what point in the patient's life the drug should be administered are important questions that need to be answered before the true effectiveness of CBD can be measured. With CBD and medical marijuana making a quick entry into the medical field and becoming an increasingly significant topic on the political agenda, improved testing techniques, more focused studies on the effectiveness of different forms of CBD, and greater involvement by clinicians will go a long way in making CBD a more viable option. Designing trials that provide concrete results in a simplified and patient-friendly way are important to the progress of CBD becoming both accepted in the medical community and getting necessary regulatory approvals. Combining the promise of this new drug with the sophisticated techniques of clinical trials and laboratory testing can help physicians feel more comfortable about prescribing CBD and patients to feel more comfortable about using CBD. The expanded

acceptance of CBD would go a long way in moving this new treatment option forward in the field of medicine.

Studies furthering the understanding of CBD's mechanism of action will be significant towards improving the design of the drug as well as its delivery and dosage scales. Throughout this study, evidence provided has assisted to uncover some of the likely mechanisms including glutamate inhibition, blocking of calcium channels, and metabolic interactions. It is likely that CBD has multiple mechanisms of actions and as such would have a broad spectrum of efficacy that is ideal towards controlling a range of seizure types and seizure severity for patients with varying symptoms or epilepsy diagnosis. With CBD acting in multiple ways, we can see that there would be a number of advantages for prescribing the drug to individuals whose seizures are not easily controlled or if their diagnosis is unclear and other AEDs are not reliable or safe to administer. We have made some general observations in this study about CBD's actions in the brain that are comparable to those made in other clinical studies. Understanding how CBD works is clinically important so that physicians can make medicinally practical decisions on whether to use CBD as a replacement drug for another AED or to add it to a patient's existing regimen.

An intended goal of this study and the associated team was to improve our knowledge of CBD as an antiepileptic compound and estimate its effectiveness in treating seizure activity in children with generalized intractable epilepsy, with the unique approach of recording both physical seizures as well as any behavior or daily function changes occurring over time. By examining these changes and understanding their occurrences we sought to provide physicians and the general public with improved

comprehension and acceptance of cannabidiol as a treatment option so that better therapeutic decisions could be made. Studies such as this assist in facilitating changes in regulations surrounding the drug and help to drive more scientific studies that look at the use of CBD and other cannabinoids for the treatment of other diseases, disabilities, and medical impairments. Of course, the true advantage of this present study is the data provided that supports the use of CBD in a population of children who have exhausted the options available to treat their debilitating seizure activity. Like most AEDs, CBD is not preventative or curative of seizure activity or epilepsy symptoms, but it is able to successfully assist in controlling the excessive hyperexcitability caused by this otherwise often drug-resistant brain disorder. We believe that improving quality of life should be the intended focus of all research involving the development and testing of any new drugs. CBD has shown the ability to reduce seizures comparable to that of other AEDs, and doing so with much less severe side effects, thus providing patients with an overall better quality of life. This study helps to provide Class III evidence that CBD (specifically that produced by GW Pharmaceuticals; Epidiolex) is well tolerated and safe for children with intractable generalized epilepsy. There is a current need from other patients, not just those with epilepsy, for more effective therapies. Studies like this go a long way to inform lawmakers, the public, physicians and other advocates of medical marijuana use of the potential drugs like this can have when they are allowed to be safely researched.

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BIOGRAPHICAL SKETCH

Christopher L. Anderson earned his Doctor of Philosophy degree in Biomedical Engineering in the spring of 2017, with a focus in epilepsy and pharmacology. Born in Cooperstown, NY February 1, 1989 he received his high-school diploma with high honors from Cherry Valley-Springfield Central School (Cherry Valley, NY). Chris then earned his Bachelor of Science in Mechanical Engineering with a Concentration in Bioengineering from the Rochester Institute of Technology in May 2012. Throughout his undergraduate career, Chris was employed as a Mechanical Engineer intern for Vanderweil Engineers, LLC (Boston, MA) and Wegmans Food Markets, Inc. (Rochester, NY). During this time he served a member of the American Society for Mechanical Engineers (ASME), the Biomedical Engineering Planning Committee, and the Society for Biomaterials.

In August 2012 Chris moved to Gainesville, Florida, where he attended the University of Florida and earned his Master of Science in Biomedical Engineering in May 2014. Chris' primary area of study was with Dr. Bryan Conrad in the Biomechanics and Motion Analysis Laboratory where his thesis focused on the "Biomechanical Comparison Between Steel and Fiber Wire When Used in Transverse Patella Fracture Fixation". Upon completion of his master's, Chris then joined the Carney Epilepsy Research Lab where he began working as a Graduate Assistant and pursued his aforementioned Doctor of Philosophy degree under the advisory of Dr. Paul Carney. Together they have worked on a number of different projects including the use of Transcranial Direct Current Stimulation (tDCS) on neonates with hypoxic ischemic encephalopathy. Their main area of research continues to be with the use of cannabinoids for pediatric epilepsy and other debilitating diseases or medical problems.

During this time, Chris has earned several awards and honors including the University of Florida Graduate Association Academic Achievement Scholarship, the NCAA Graduate Student Research Grant, was a Pruitt Biomedical Engineering Research Day Presentation Finalist, a National Institute of Health Office of Extramural Research Participant, and was given the Southeastern Association for Housing Officers Graduate Student Award

While completing his Ph.D., Chris has worked for the University of Florida Health Pediatrics Department as a Clinical Study Coordinator and for the University of North Carolina at Chapel Hill Neurology Department as a Clinical Research Engineer. Chris is currently a member of the Florida Engineers Society (FES), American Epilepsy Society, Biomedical Engineering Society, and the Biomaterials Society at UF. These opportunities and the shared experiences of his committee members have provided him with valuable insight to the design, coordination, and implementation of a number of different research projects. In the short term, Chris is looking forward to continuing his work with Dr. Paul Carney as an engineer/research consultant, with the overall goal to continue the advancement of cannabis medicine and work to improve the quality of life for patients in desperate need of new treatment. Outside of academics, Chris is very involved in University activities. He has worked as a Graduate Housing Director for the University of Florida Department of Housing and Residence Education and a Specialist Tutor for the UF Athletics Association. Chris enjoys live music, hiking, biking, skiing, and especially attending any University of Florida Gator athletic events.