Weaving Charlotte's Web: An In-Depth Guide to Cannabidiol

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Weaving Charlotte’s Web: An In-Depth Review of Cannabidiol

By

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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College

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ABSTRACT

Cannabidiol, also known as CBD, first gathered national spotlight after Charlotte Figi and her mother Paige were able to find two physicians willing to prescribe CBD to treat Charlotte’s seizures. Charlotte suffered from Dravet Syndrome, but was able to find relief from CBD, which decreased the number and severity of her seizures. This sparked national interest and was the catalyst that lead to research and changes surrounding CBD uses and legality. Cannabidiol is a single cannabinoid that is found within the Cannabis sativa plant family—the same family that includes marijuana. This cannabinoid differs from tetrahydrocannabinol (THC) and does not provide a high to its users, which depends on the receptors activated by each cannabinoid.

To date, Epidiolex® is the only FDA approved drug which contains non-synthetic cannabidiol extract. The drug has a very narrow indication and is approved only for rare forms of pediatric seizures such as Lennox-Gastaut Syndrome and Dravet Syndrome. Non-FDA-approved uses of CBD vary based on anecdotal evidence. Some commonly reported uses for CBD include easing anxiety, helping with sleep, and clearing up acne or skin blemishes. Thousands of CBD products that do not have FDA approval are on the market and are available to consumers. This largely came about due to the passage of the 2018 Farm Bill, which made hemp federally legal in the United States—essentially federally legalizing CBD. However, not all states have legalized all forms of CBD.

For example, Mississippi enacted Harper Grace’s Law in 2014 which approves cannabidiol in limited quantities and indications if prescribed by a licensed physician. It also led to clinical trials for CBD in epilepsy to be conducted at the University of
Mississippi Medical Center in Jackson, Mississippi, presumably for a competitor product of Epidiolex®. However, no other CBD products are legal for use in Mississippi, despite the prevalence of CBD stores and CBD products in state-permitted pharmacies. Things may change, however, as Mississippi is set to have medical marijuana on its ballot in November of 2020. If passed, this would not only allow medical marijuana to be prescribed for certain medical indications, but presumably CBD as well.
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<td>DEA</td>
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<td>Endocannabinoid System</td>
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<td>NIH</td>
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<td>PTSD</td>
<td>Post-Traumatic Stress Disorder</td>
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<td>THC</td>
<td>Tetrahydrocannabinol</td>
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<td>UMMC</td>
<td>University of Mississippi Medical Center</td>
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INTRODUCTION

*Charlotte’s Web*

Charlotte Figi was one of two children born to Paige Figi on October 18, 2006. Charlotte and her twin brother were born healthy and happy. Then three months later Charlotte began having seizures. Her first seizure was 30 minutes long, but soon her seizures would last hours and frequently land her in the hospital. No doctor could give her a diagnosis. No tests were coming back with positive results. Yet, Charlotte was still having constant seizures, and the seizures were becoming increasingly severe in length and strength. Finally, one doctor suggested that Charlotte might have Dravet Syndrome. Dravet syndrome is an exceptionally rare case of intractable epilepsy. This was the first attempt at a diagnosis for Charlotte and soon she was seeing a neurologist at the Children’s Hospital in Colorado who conducted a scan for the SCN1A gene mutation which is common in Dravet syndrome cases. For the first time, a test came back positive. As devastating a diagnosis as it was, Charlotte’s mother, Paige, was relieved to finally have an answer. Now she could finally go about finding the next step to help her daughter. A Dravet Syndrome specialist in Chicago suggested Charlotte begin a ketogenic diet, which is high in fat and low in carbs. This would cause her body to produce more ketones which naturally suppress seizures (Young).

At first there was a noticeable drop in the number of seizures Charlotte had. However, there was also a noticeable decrease in her bone density and she experienced reduced immunity. Two years into the diet, her seizures came back. Paige
began researching anything and everything having to do with Charlotte’s condition. She happened upon an article about a boy from California treating his Dravet syndrome with cannabis. At first Paige was hesitant, but when weighing her options, she decided it was worth trying. The cannabis used for treatment was high in CBD and low in THC, both different cannabinoids of marijuana. Colorado approved the legalization of marijuana for eight medical purposes in 2000, one of those purposes being seizures. Paige decided to apply for the program and plead Charlotte’s case. It was no easy pitch. Because she was so young (5 years old at the time) no doctor was willing to sign off on it because of her age and the unknown long-term results. After searching, she found two doctors willing to approve her program application for the same reason as Paige was willing to apply—nothing else had worked. Once approved, the results were stunning. Charlotte’s seizures slowed to two or three times a month, mostly in her sleep. She regained her immune system and bone density and began developing normally. She continues to take two doses a day with her meals. The strain of cannabis used to treat her, R4, was named Charlotte’s Web, representing the tangled path she went through to find a cure for her seizures (Young).

What is CBD?

Cannabidiol, or CBD as it is commonly known, is a specific cannabinoid found in plants from the *Cannabis sativa* family, such as hemp and marijuana. Cannabinoids, sometimes also referred to as phytocannabinoids, are naturally occurring chemical substances which possess biological activity (Merriam-Webster). Cannabinoids such as CBD are chemicals produced by the flowers of the cannabis plant that emulate some of the natural neurotransmitters of the body, endocannabinoids (Rahn). Endocannabinoids,
which are present in all vertebrates, are responsible in part for maintaining the homeostasis of our bodies (UCLA Health). The endocannabinoid system (ECS) helps mediate the internal cell to cell communication and aids in the stabilization of a variety of body processes such as metabolism, memory, appetite, stress, pain and sleep (Rahn, UCLA Health). Endocannabinoids bind to receptors located throughout our bodies. The receptors are generally divided into Cannabinoid-1 Receptors (CB1) and Cannabinoid-2 Receptors (CB2). The central nervous system, consisting of the brain and nerves, houses the CB1 receptors while the remainder of the body houses the CB2 receptors. Understanding how our endocannabinoid system works, including how our receptors work, has allowed for distinctions to be made among the many various cannabinoids.

The two most common cannabinoids are CBD and THC, known as cannabidiol and tetrahydrocannabinol respectively. THC is the main psychoactive cannabinoid in marijuana and other Cannabis sativa plants which provides a “high” to its users (Holland). This high is present because of THC’s ability to tightly bind CB1 receptors in the central nervous system, specifically the brain. THC and CBD have very similar structures and are in fact made up of the exact same composition of elements, only arranged slightly differently (Holland). Both structures are similar to natural endocannabinoids made by the body and allow for interaction with CB1 and CB2 receptors. Due to the differences in structures, THC has more of an affinity for the CB1 receptors and CBD has more of an affinity for the CB2 receptors. It is unknown for certain if CBD will bind directly to the CB1 receptors in the central nervous system, but it is known that CBD will interact indirectly, lessening the effects of THC and reducing epileptic seizures (Project CBD). CBD is currently being examined for its medicinal
properties and as an alternative to other medications for conditions such as chronic pain, seizures, sleep-disorders, and many more. Currently, Epidiolex® is the only FDA approved drug on the market containing actual cannabidiol (CBD) from the Cannabis plant. This approval came on June 25 of 2018, and Epidiolex® is specifically indicated for treatment of two rare and severe forms of pediatric epilepsy, Lennox-Gastaut Syndrome and Dravet Syndrome, in patients at least 2 years of age (Commissioner, Project CBD). There are other drugs on the market such as Marinol, Nabilone, and Rimonabant which are synthetic cannabinoid drugs that mimic other cannabinoids and endocannabinoids, but the active components in these medicines are not derived directly from the Cannabis plant like the phytocannabinoids in Epidiolex® (Rahn).

Non-FDA approved products containing CBD are available as supplements and vitamins, marketed towards curing various ailments, soothing aches and pains, and even clearing skin. Among these products consumers will commonly encounter terminology such as “CBD rich” and “CBD dominant.” While similar sounding, these terms are used to distinguish differing amounts of THC in products by comparing ratios of CBD:THC. A product labelled “CBD-rich” has high CBD and THC contents, but there is usually more CBD than THC (about 4% more dry weight) (Rahn). A product labelled “CBD-dominant” on the other hand refers to products with an overwhelming amount of CBD and minimal THC content.

**Terms and Classifications**

Many terms surrounding CBD are used interchangeably, but are actually distinct and separate terms and need to be defined. The most common terms are hemp, cannabis, marijuana, and weed. Cannabaceae, the hemp family, includes the Cannabis genus under
which distinct species such as Cannabis L. (hemp) and Cannabis sativa L. (marijuana) fall (Classification). Cannabis the genus can be thought of as a general, encompassing term that contains multiple subsets including marijuana and hemp (CBD Web). Between these two, the most easily quantifiable distinction comes with how much THC is present in the plant. Anything greater than 0.3% THC dry weight qualifies as marijuana. Anything less than 0.3% THC dry weight qualifies as hemp. Because THC is mainly produced in the flowering parts of the Cannabis plants, US law denotes hemp as the stalks, stems, and sterilized seeds of cannabis sativa and marijuana as the leaves, flowers and viable seeds of Cannabis sativa (Stanford). Weed is one of many slang words referring to marijuana which has origins in 1930s Harlem, but does not refer to a specific species at all (Wright).

Scheduling of substances directly relates to their potential for abuse and dependence and is listed on a scale from I-V with I having the highest potential for abuse and physiological and psychological dependence and 5 having the least (DEA). Cannabis has previously been listed as a Schedule I drug since 1970, which implies that there is currently no medical value or accepted reason for using the substance (DEA).

**Hypothesis**

The purpose of this narrative review is to determine if the following hypothesis can be supported: *That CBD has potential to clinically treat numerous conditions, but that such potential needs to be explored in a rigorous and legal way.*

**Data Collection**

Data for this review comes from easily accessible information which is available to the public. Most of my data can be found online, through various websites that are
sited throughout this paper and can be found in the references section. Other data came from magazine readings, advertisements, and personal observations and interactions. My interactions included informally interviewing store owners who stocked and sold CBD products, as well as speaking with people who are currently using CBD for their personal health in some way. These personal anecdotes were compared to anecdotal evidence from additional online sources.
THERAPEUTIC USES OF CANNABIDIOL

Clinical Uses of CBD

Cannabidiol is marketed to heal and improve many ailments, but what does CBD really treat? There are many personal anecdotes documenting the potential uses of CBD, but clinical studies and clinical data on cannabidiol are fairly limited. The most substantial clinical data comes from clinical trials related to the treatment of epilepsy which lead to the FDA approval of Epidiolex® in June of 2018 (Centers for Drug Evaluation and Research). An interesting clinical study investigated the effects of the human endocannabinoid system as a cancer target. The results could have implications in the use of CBD as a cancer therapy, since CBD interacts with the body’s natural endocannabinoid system receptors CB1 and CB2 (Laezza, et al.) However, this preliminary data needs to be researched more before drawing firm conclusions. Sativex is a new investigational drug currently in clinical trials which aims to reduce pain in cancer patients with a poor response to opioid medications. Sativex has THC as well as CBD components (GW Pharmaceuticals).

There have also been a few pre-clinical studies to explore the effectiveness of CBD in neurological diseases such as Alzheimer's Disease, Parkinson’s Disease, and Multiple Sclerosis (Mannucci, et al.). The findings suggested that because of the anti-inflammatory qualities of CBD and the antioxidant properties, CBD could be a breakthrough in neuroprotective agents, but there would need to be clinical studies conducted and more data found before this could be confirmed (Mannucci, et al.). Below is a 2019 chart from Hemp Industry Daily, which shows highlights the pharmaceutical
interest in clinical research of cannabidiol as well as which companies have completed, active, or future study trials lined up. GW Pharmaceuticals currently has the highest number of completed trials and is the company that completed clinical trials for Epidiolex®. GW pharmaceuticals is also the company currently conducting trials for Sativex.

![Figure 1: US Pharmaceutical Companies](https://hempindustrydaily.com/hemp-cbd-companies-lining-up-university-research-to-validate-anecdotal-evidence/)

The current clinical data on the uses of CBD is fairly limited, which has led to increased attention on personal anecdotes of success/treatment with CBD and products containing CBD. A lot of information circulating through the general population concerning the medicinal properties of CBD come from personal testimonies of how the compound has worked to fix their problems. There are common trends and abundant
stories of CBD helping with the same conditions, such as anxiety, sleep disorders, and chronic pain, to list a few. Despite the wide array of potential treatments, CBD surprisingly is not reported to have many side effects. These anecdotal stories provide a starting point to begin researching the effects of CBD in a clinical setting to determine the true range of this drug. A few examples from Centennial Spotlight include stories on how CBD helps with:

- Improved sleep
- Reducing aches and pains, arthritis, post-workouts
- Anti-inflammatory skin care creams, anti-aging creams
- Relaxing, reducing anxiety and stress, PTSD alleviation

While none of these are confirmed indications for the use of cannabidiol (currently seizures are the only medically acceptable indication with clinical data), it is interesting to notice how the general population is seeing effects of cannabidiol in their everyday lives (Centennial Spotlight). Although none of these anecdotal stories are backed by clinical data as of now, they may pave the way for new areas of research related to the uses and benefits of CBD.

*Epidiolex*®

*Epidiolex*, the only FDA approved drug containing non-synthetic CBD derived directly from Cannabis plants, is indicated for two severe and rare forms of pediatric epilepsy, Dravet syndrome and Lennox-Gastaut syndrome (Center for Drug Evaluation and Research). This schedule V drug is approved in patients over 2 years of age and is available as a liquid solution which is to be taken twice daily for seizure control (Slowiczek). Doses are based on a patient’s weight, severity of seizures, and tolerability
of the drug. Doses can be increased if needed, but it is recommended to start at a low
dose to gauge patient response. The clinical studies results showed a statistically
significant (p value of 0.001) decrease in seizures for patients taking Epidiolex® than for
patients on a placebo. This clinical study did not take into account race because 86
percent of participants were white, but was shown to work similarly in males and females
and to work similarly in those above and below the age of 18. There were four clinical
trials that led to the approval of Epidiolex® by the FDA. Double-blind clinical trials
(neither health care provider or patient knew what drug was being received) were done in
Europe and the US and consisted of 550 patients over 58 sites. The patients were about
50/50 male to female (real values are 46/54 M/F).

How were the trials designed? Epidiolex® was evaluated throughout four clinical
trials; the first three evaluated safety and efficacy, the fourth was purely testing for the
safety of the drug. The subjects/patients in the first two trials suffered from Lennox-
Gastaut syndrome and were having uncontrolled seizures due to lack of effectiveness on
their current treatments. These subjects were assigned randomly into a treatment and
placebo group in a double-blind study. Both groups took two doses per day, and doses
for both groups were increased every other day for two weeks to reach the desired
dose. After reaching the desired dose, subjects remained there for 12 weeks. The
difference in the number of seizures between the placebo and treatment group and their
respective baselines were measured and used to determine the efficacy of Epidiolex®.

Trials three and four were conducted for patients who suffered from uncontrolled
seizures on their current medication for Dravet syndrome. Trial 3 was conducted the
exact same as trials 1 and 2, but for patients with Dravet syndrome. Trial 4 was a study
to determine the safety and side effects of certain doses of Epidiolex®. In this double-blind study, subjects were randomly assigned to take one of three possible doses of Epidiolex® twice daily for 3 weeks.

Mild and severe side effects may occur when taking Epidiolex®. Because Epidiolex® was approved through clinical studies, these side effects are known. Mild side effects include feeling drowsy or lacking energy, generally feeling under-the-weather, loss of appetite, and diarrhea. Mild side effects are expected to lessen over the course of a few days to a couple of weeks. While severe side effects of Epidiolex® are rare, reported side effects included sedation, liver problems, severe allergic reactions, and suicidal thoughts (Slowiczek). The risk of most side effects is increased with higher doses of Epidiolex®.

**CBD and Animals**

There are no currently approved cannabidiol containing drugs for animals. While many people use CBD for anxiety and other common conditions of animals, it is currently illegal under the Food, Drug, and Cosmetic Act (FDCA). The FDCA states that any product containing CBD, THC, or other components of marijuana are currently not allowed in food of any sort for human or animal consumption (FDA). As far as veterinary recommendations, the topic must be brought up by the patient before the vet may endorse trying CBD products for pets (Consumer Reports). If looking to try cannabidiol for a pet, recommendations are to seek out products marketed for animals that avoid other ingredients which may be toxic to animals. Other recommendations include dosing gradually and watching to see how each pet responds individually to treatment with CBD. Currently there is even less known about the safety and
effectiveness of CBD in animals than there is in humans. This is an emerging market which is expanding as pet owners’ anecdotal stories of pets with lessened anxiety, improved movement due to decreased pain of arthritis, and decreased seizure activity grow (Consumer Reports).
FEDERAL REGULATION OF CANNABIDIOL

Overview

While CBD is found virtually everywhere now, ranging from gas stations to dispensaries to CBD specific stores, the legality surrounding CBD is not clear. There is a lot of uncertainty on which laws apply in which states and where the ever-changing fine line between legal and illegal stands.

Agricultural Improvement Act of 2018 (2018 Farm Bill)

Every five years, Congress passes a bill stating and amending policies governing national agriculture, nutrition, conservation, and forestry. The Agricultural Improvement Act of 2018 is the current version, which will last through 2023. It is often cited and commonly known as the “2018 Farm Bill.” This bill is of interest because of the extent to which hemp is included and discussed. The term “hemp” appears 48 times throughout the 2018 Farm Bill.

The term hemp is clearly defined in section 11101 of Title 11 and references section 297A of the Agricultural Marketability Act of 1946 which states that hemp is defined as any part of the plant Cannabis sativa L. with less than 0.3% delta-9 tetrahydrocannabinol (THC) concentration by dry weight. A key distinction concerning definitions is addressed later in section 12608 of Title 12, where it is noted that hemp does not include “marihuana” and that the Schedule 1 status of tetrahydrocannabinol (THC), found in the Controlled Substances Act, will not apply to the minimal amount of THC found in hemp as it was defined earlier. After clarifying the definition of hemp, sections 11101, 11106, 11112 and 11120 of Title 11 all make varying amendments to
include hemp under crop insurance (Agricultural Hemp Solutions). This extension protects farmers under the Federal Crop Insurance Act which assists farmers in production and crop termination or crop failure (Hudak).

The 2018 Farm Bill amends the Agricultural Marketing Act of 1946 to allow states a chance to propose a plan for growing and producing hemp, which can then be sent to the United States Department of Agriculture (USDA) for approval. In order for the USDA to approve a state’s proposed plan, the plan must state where the hemp will be grown, how the THC levels will be tested, and how plants with THC levels exceeding 0.3% will be disposed of. If approved, that state may then grow hemp. If denied, that state must comply with federal laws and regulations (United States Senate Committee on Agriculture, Nutrition, and Forestry).

Research involving hemp is addressed in sections 7415 and 7125 of Title 7. Section 7415 deals with the legitimacy of industrial hemp research and requires a study and report on the “economic viability” of the hemp industry (domestic production and sales of industrial hemp) in the United States. Section 7125 has been changed to include hemp in alternative and supplemental crops on which research projects can be conducted. It is important to note that while the 2018 Farm Bill does make changes to the production of hemp and allow research, it specifically notes in section 10112 that those amendments do not authorize interference with current laws on interstate commerce regarding hemp.

The 2018 Farm Bill provides a clear definition of hemp, allows growth and production of hemp if through a USDA approved plan, extends protection for researchers and farmers who choose to work with hemp, and legalizes hemp under specific conditions and with considerable restrictions and regulations (United States Senate
Committee on Agriculture, Nutrition, and Forestry). This bill does not have anything to do with state-legal cannabis programs, which are still illegal under federal law (Hudak). In regards to cannabidiol (CBD), this bill removes hemp-derived products from Schedule I status, which effectively legalizes CBD. However, nowhere is it explicitly stated that CBD is legalized. In fact, according to the 2018 Farm Bill, only very specific batches of CBD would be considered legal. Only CBD produced following every part of this bill, following all federal and state regulations, and produced by a licensed grower would be considered legal. Any other form of CBD products (even if produced under state-legal or medical cannabis programs) are considered illegal under federal law (Hudak). This is a gray area where technicalities are difficult to enforce, and manually determining the origin of all CBD-containing products is unrealistic. Another gray area is that although the 2018 Farm Bill essentially legalized CBD, most CBD products are still in violation of the Food Drug, and Cosmetic Act.

**Food, Drug, and Cosmetic Act**

The Food, Drug, and Cosmetic Act (FDCA) is a set of laws giving the FDA authority to monitor the safety of foods, drugs, medical equipment, and cosmetics that was enacted by Congress in 1938 (Wikipedia). The FDA website has stated that it has only approved one drug containing CBD, Epidiolex®, and specifically notes that it is currently illegal to market and sell CBD in addition to food or by labeling it as a dietary supplement (FDA). The website also notes that CBD products are being marketed without proven health benefits, with potentially untrue claims, and under unknown quality, but makes a specific point to mention food. The FDA strongly encourages pregnant women to avoid any form of marijuana while pregnant (including THC and
CBD isolates). The U.S. Surgeon General advised to avoid THC since the substance may cross into the placenta and affect fetal brain development as well as linger in breastmilk. There is no conclusive evidence on CBD, so it is recommended for mothers to avoid it as well.

Interstate commerce of CBD or THC directly violates the Food, Drug, and Cosmetic Act. Under the Q&A section of their website, the FDA states that food with an active drug ingredient of an approved drug or ingredients which are currently under clinical investigation are prohibited from interstate commerce. This is interesting when taken into account with internet sales of CBD. For the most part the FDA has been turning a blind eye and companies like Oki are being crafty with marketing, labeling their CBD-infused waters as having “active hemp ingredients” (Reiley). However, the FDA sent out twenty-two warning letters to companies in 2019.

Warning Letters from the FDA

The FDA website has a list of companies to which it has issued warning letters concerning unapproved new drugs and supplements which contain cannabidiol. Most recently updated in November of 2019, the FDA sent letters to a total of twenty-two companies located in California, Texas, Oklahoma, Colorado, New York, Oregon, Florida, North Carolina, Arizona, Kentucky, Arkansas, Maine, New Jersey, and Washington for that calendar year (FDA). Companies marketing products with unapproved claims or untested amounts of CBD were sent a letter addressing the marketing and selling of cannabidiol products. As an example, the letter to Koi CBD LLC in California was sent a letter on the 22th of November 2019 and followed the following format.
The warning letter began by addressing the products of interest by name and the claims of each product. The next issue to be covered was the misbranding of CBD containing products under varying sections of the Food, Drug, and Cosmetic Act (FDCA). Koi CBD LLC was also selling CBD products targeted to treat animals, which was in violation of the FDCA. The letter goes on to mention violation of interstate commerce law under the FDCA and the labeling and definition restrictions for dietary supplements, which CBD does not currently fall under. The next header is titled “Unapproved New Drugs” and notes specific instances on Koi CBD LLC’s website which claim to know and promote benefits of CBD. Lastly, the warning letter addresses adulterated human and animal foods. Each letter follows this same general outline.

Although these warning letters were sent out, the FDA still struggles to enforce certain rules on companies that choose to market CBD products. Dr. Amy Abernethy, principal deputy commissioner of the FDA and co-chair of CBD Policy Working group founded by the FDA, noted two important points in her testimony to Senate Agriculture Committee on July 25 of 2019. First, she acknowledged that full regulation of CBD products as ingredients in food or supplements would require new laws from Congress, which could likely take up to five years to form and pass (Page). Second, she implied that the FDA was hesitant to legitimize current over the counter CBD products. This would decrease the need for prescription drugs like Epidiolex®, which would deter pharmaceutical companies from investing in the research to determine the full extent of what CBD could treat or help cure. There is not enough current research available for the FDA to determine the safety and efficacy of CBD for certain populations and ailments, so pharmaceutical companies’ interest in the product is necessary to drive clinical trials.
Dr. Abernethy did concede that for the most part the FDA is turning a blind eye to the current CBD industry and is mainly focused on enforcing laws related to the marketing of cannabidiol. Products containing CBD which are marketed with “unsubstantiated therapeutic claims” are the main concern of the FDA at this time.
STATE REGULATION OF CANNABIDIOL

Just like with medical and recreational marijuana, states vary in their allowance of consumer use of CBD.

**Figure 2: US State Legalization Map**

From: [https://commons.wikimedia.org/w/index.php?curid=2370050](https://commons.wikimedia.org/w/index.php?curid=2370050)

This is a current map as of 28 March 2020, from Wikipedia. The blue states have fully legalized marijuana including CBD, while the green states will allow marijuana to
be used for medical purposes. Differentiating between the green states, the light green states have legalized medical marijuana use as long as there is a low level of THC (indicating high levels of CBD), while the dark green states are unconcerned with the amount of THC. Finally, the gray states have not legalized marijuana or cannabidiol in any form, adult use or medical use. The states marked with a red letter D have decriminalized marijuana including cannabidiol (Wikipedia).

**Special State Laws of Interest**

While most states have legalized hemp-derived CBD for seizures and epilepsy after the Farm Bill was revised in 2018, each state has its own particular rules and regulations regarding cannabidiol. The source (hemp or marijuana), as well as the percentages of THC and CBD, and indications of CBD are the main categories to vary depending on the state.

California has legalized CBD for medical and recreational use, but prohibits the addition of CBD as a food ingredient until approved by the FDA as a safe ingredient, additive or supplement (CBD Project Awareness). This rule applies to food intended for human consumption as well as animal or pet consumption. An interesting way current businesses are evading this rule is by offering CBD as a side item on menus. A CBD shot can be ordered and added to food or drink by the customer. This is occurring in other states as well such as New York.

Delaware has also legalized medical use of CBD from hemp and marijuana but requires all patients as well as their caregivers to have an ID card that allows them to possess a maximum of 6 ounces of CBD. The medical CBD from marijuana cannot have any more than 7% THC. South Carolina however, requires CBD products to have 98%
CBD and only 0.9% of THC (CBD Project Awareness). This is an area in which states vary greatly on what is allowed. Hemp by definition in the 2018 Farm Bill is a strain of cannabis which has less than 0.3% THC; however, especially with states that have legalized CBD from marijuana this value varies.

Minnesota and New Mexico have added specific qualifying medical conditions to their lists of approved reasons for prescribing CBD. A few of the usual conditions include epilepsy, end-stage cancer, multiple sclerosis and Parkinson’s disease. Minnesota approved CBD for Alzheimer’s and obstructive sleep apnea while New Mexico was the first state to approve CBD for post-traumatic stress disorder (PTSD) patients (CBD Project Awareness).

Idaho is one of three states that currently has restrictions on all forms of cannabis and CBD, even after the 2018 Farm Bill which legalized hemp on a federal level. Epidiolex®, the only FDA approved drug containing CBD, is the only exception to this rule. This creates a significant gray area for Idaho citizens who may be able to use CBD legally under federal law but not under state law (CBD Project Awareness).
MISSISSIPPI REGULATION OF CBD

Harper Grace’s Law

Just as Charlotte Figi was the catalyst for change at the national level, Harper Grace Durval was the catalyst for change at the state level in Mississippi. Harper Grace Durval began having seizures around 6 months of age and was diagnosed with Dravet Syndrome—the same diagnosis that Charlotte received (Gates). Harper Grace’s mother, Ashley Durval, advocated for the legalization of CBD treatments in Mississippi for epileptic seizure patients like her daughter. She stated that the current medications simply do not work and that they are quickly running out of options for anti-seizure medicines (WMC-TV).

Harper Grace’s condition and Ashley Durval’s persistence in advocating for CBD use for severe epileptic patients in Mississippi ultimately lead to the passing of Harper Grace’s Law, signed into law in April of 2014 by Governor Phil Bryant (Wikipedia). It originated as House Bill 1231 and passed with a majority vote in both the House and Senate. Harper Grace’s Law allows cannabidiol in very limited context to be obtained from a physician who is licensed to practice in Mississippi. The CBD allowed can be in either oil or resin form from a cannabis plant with at least 15% cannabidiol for oils or 50 mg of cannabidiol per milliliter for diluted resins and a maximum of 0.5% tetrahydrocannabinol or THC content (Mississippi Legislature, Wikipedia). Additionally, the CBD must be obtained or tested specifically through the National Center for Natural Products Research located at the University of Mississippi and be dispensed by the pharmacy at the University of Mississippi Medical Center in Jackson, Mississippi. The
law is reserved for patients with “debilitating epileptic condition(s)” (FindLaw). Harper Grace’s Law is one of the stricter laws regarding medicinal cannabis use among the states that have approved CBD for medical purposes (Wikipedia).

**UMMC Clinical Trial**

As of 2017, even after the passing of Harper Grace’s Law, Mississippi still did not have the final approval needed from the federal government to begin clinical trials at the University of Mississippi Medical Center (UMMC) in Jackson, Mississippi (Gates). Dr. Brad Ingram, the director of the Pediatric Comprehensive Epilepsy Center at UMMC, would be the one to oversee a small trial (roughly 5-10 patients) of CBD oil in severe seizures of young children if the 32-page proposal submitted to the FDA were approved (Gates). He noted that while a lot of work had gone into creating the proposal, federal approval is ultimately out of anyone’s hands. The approval process includes three federal agencies: The National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Drug Enforcement Agency (DEA).

Then in November of 2018 and UMMC had received the necessary approval from the DEA and FDA to begin trials. Dr. Ingram stated that the study would be six months long with a maximum of ten patients and aimed to treat the “sickest of the sick” with “compassionate care” (Oeth). A secondary consideration with a short, small trial was that of product availability after the study. No one wants to be given a drug that works and then told that they will no longer have access to CBD. Once the cannabidiol is produced and checked for quality, it is diluted and dosed using pharmaceutical grade sesame seed oil (Oeth). The study produced excellent results, with most patients experiencing a drop in the number of seizures per month and all experiencing an
increased quality of life. The current drug and dosages were not seen to cause any 
damage to developing brains or tolerability issues in the patients. This clinical trial has 
been granted a one-year extension in the summer of 2019 and will be reassessed in the 
summer of 2020. The FDA extension will allow more development of treatments for 
epileptic seizure patients who have not had success with traditional seizure drugs (Oeth).

Technically, this trial provides the only current legal access to cannabidiol in 
Mississippi. So why are there so many products and stores openly selling and promoting 
CBD products, even in local pharmacies? This is the gray area of law where enforcement 
(or lack thereof), specific marketing, purity, and definitions all come into play.

**Medical Marijuana on Mississippi November Ballot**

Following all of the attention medical marijuana and CBD have gathered over the 
past few years, Mississippi will have Medical Marijuana on the ballot in November of 
2020. The group Mississippians for Compassionate Care began an initiative that 
gathered 106,000 signatures, more than the 86,000 signatures required, to form Ballot 
Initiative 65 which is sponsored by Ashley Durval (Ramseth). The goal is to legalize 
medical marijuana use in Mississippi allowing doctors to prescribe for specified 
conditions including cancer, epilepsy, multiple sclerosis, and Parkinson’s. If approved, 
the Department of Health would regulate medical marijuana treatment centers and 
dispensaries. While 77% of Mississippians seem to be in favor of legalizing marijuana 
for medical purposes, a few concerns have been raised about the medical legalization 
eventually leading to recreational legalization (Ramseth). The other opposing arguments 
are that little is known about marijuana and how it interacts with certain medical 
conditions.
CONCLUSION

Cannabidiol holds promise for many different conditions but requires more clinical testing and research before any conclusions can be drawn. The data explored in this paper in part, support the hypothesis that CBD holds clinical promise for the treatment of conditions, and studies are being conducted in a rigorous way that meets FDA approval in the example of Epidiolex® or may do so in the future such as the CBD product in clinical trials here at the University of Mississippi. But we also reviewed accounts of situations whereby CBD is not always being used for clinical conditions that have support or rigorous studies, or is CBD being used in compliance with local laws, such as in the state of Mississippi.

The implications of future approvals of CBD are closer than we think. As this drug becomes more regulated and available from pharmacies, it will be necessary for physicians and pharmacists to have a current working knowledge of the topic and laws surrounding CBD as well as the available forms and dosing issues in order to ensure the best possible patient care.
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