Why Study Marijuana? Mapping Out the Importance and Barriers to Cannabis Research.

An Honors Thesis (HONR 499)

by

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Abstract

Cannabis is one of oldest cultivated plants used for medicinal purposes. The landscape of medical *cannabis* is rapidly expanding as more and more people push for its legalization. However, law-makers and politicians depress *cannabis* potential, claiming there is not enough evidence-based science behind the substance to convince them. Yet, in the United States, in order to study *cannabis*, the research has to be approved by multiple federal agencies through a rigorous and expensive processes. The federal barriers suppressing *cannabis* research and the government's continuous call for *cannabis* prohibition has more ripple effects than expected. *Cannabis* prohibition affects the discovery of health benefits and risks of *cannabis*. Physicians, health professionals, and patients are advising dosages and types of *cannabis* without possessing the adequate knowledge, and without knowing the potential risks involved. As the acceptance and usage of *cannabis* and continues to grow in the United States, the demand for a more complete understanding on the substance is required. Until *cannabis* is rescheduled by the federal government, research will continue to be neglected and America will remain in the dark on mechanism, dosages, cannabinoids and many other uncertain aspects hidden within the complexity of *cannabis*.

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Process Analysis Statement

I did not know what "weed" was until I was a freshman in high school. It was everywhere; parties, concerts, parks, and even in my all-girls, private catholic school where girls managed to take a smoke break at lunch. However, I stayed far away. I was told that *cannabis* slowed down brain function, especially in girls. It could make you stupid, lazy, and depressed. Once recreational *cannabis* became legalized in 2012, old McDonald's and abandoned buildings were turned into dispensaries and I was horrified: how was this horrible drug legal and able to be sold like liquor in a liquor store?

It was not until I came back from freshman year of college that I completely changed my opinion. I saw how *cannabis* was helping my friends with their anxiety and depression. I saw how it was changing the lives of my mother's friends with uncontrollable chronic pain. Creams, oils and lotions with cannabinol (CBD) took away muscle spasms. My town was booming from the influx of revenue that *cannabis* sales brought. I saw first-hand that all of the warning I received before were not completely true. The negative stigma that I harbored for years rapidly disappeared as *cannabis* configured into a normality and a part of my community.

When I reflect back on how I felt about *cannabis* years ago, I am baffled: I used to hate, judge and shame people for partaking in it, but now, I am almost an advocate for it. For my honors thesis, I wanted to address those individuals whom I used to be like. For those who have a negative stigma regarding *cannabis*, I want to educate you. It is not my intention to force you to change your mind or tell you that you are wrong, I want to provide you with correct information, data, and trial evidence. I want to provide you the knowledge so that you can formulate your own opinion about *cannabis*. In addition, I wanted to highlight the repercussions of *cannabis* prohibition that are not normally talked about. Due to the restrictive federal drug laws on

cannabis, research and medical application is limited. We are unable to discover all of the potential health benefits that *cannabis* has to offer but most importantly, unable to understand and obtain a final consensus on the positive and negative side effects of *cannabis*.

It is often forgotten the other goal of *cannabis* research is working towards an incredibly important cause: ending prohibition. Prohibition of *cannabis* has allotted for crime, drug production and distribution to be in control of criminals, unsafe substances that can contain and have adverse health effects and made room for a black-market. If the barriers of *cannabis* research are lowered, we will finally be able to fully understand what this substance, *cannabis*, truly is.

THE ANCIENT PLANT

As one of humanity's oldest cultivated crops, *cannabis* has a long and entwined historical geography. The exact origins of *cannabis* are uncertain but analyzation of botanical, ecological and archeological evidence suggests humans used *cannabis* thousands of years ago.

Cannabis in Central China

Hypothetical human use of *cannabis* can be traced all the way back to Central Asia. Ancient Chinese literature details how *cannabis* was domesticated from wild plants and cultivated into crops to be used as a source of food and textile fiber. *Cannabis* thrived in the favorable sunny, moist, well-drained and nutrient-packed soil. The fiber of the *cannabis* plant, hemp, was extracted from the stem and used to make rope, strong fabrics for clothing, fish-nets and paper. In 2727 BC, the Chinese Emperor, Shen-Nung, discovered the medicinal properties of *cannabis* and implemented them into his community. Shen-Nung was known to exploit various medicinal plants and other drugs derived from animals, minerals and vegetables to treat and cure illnesses. The widely considered "Father of Chinese Medicine"[9] used *cannabis* and its seeds to treat aliments such as female menstruation, malaria, constipation and absent mindedness[1]. *Cannabis* was not used as a psychoactive drug during this time. Available literature does not reference explicit drug effects of the plant; poems, writings and medical texts honor *cannabis* solely for its' medicinal properties. Shen-Nung is one of the first credited to discover the medicinal healing properties of *cannabis*. After Shen-Nung, *cannabis* became a stable in Chinese medicine for thousands of years.

Ancient Chinese texts also refer to *cannabis* as a source of food. The same seed that was used to treat various illnesses and diseases could be ingested for its high nutritional value.

Legend claims that Buddha himself ate only one hemp seed a day and survived six years under the Bo Tree while he awaited enlightenment[1].

From China, *cannabis* then spread to India and became integral in their religion. *Cannabis* was deemed one of the five sacred plants used for "freedom from distress". In the ancient Hindu scriptures, the Vedas, cannabis or "bhang" is described as a liberator and a source of happiness and joy. It was given to people to help attain delight and eradicate their fears[1]. Additionally, it was believed to be the Hindu God, Shiva's, favorite food. *Cannabis* was typically ingested as a drink or smoked as a communal activity.

European Trade

Wild *cannabis* most likely diffused into Europe 3,500 years ago through Scythians as they moved from Central Asia through Russia[34]. However, it was not until the late 1700's that it became a commodity of interest. *Cannabis* was reintroduced to Europe from the British East India Trading Company. Hemp from *cannabis*, along with other drugs such as opium, were goods traded from the East, Southeast Asia and India to England. William Brooke O'Shaughnessy, an Irish physician, learned about the medicinal uses of *cannabis* while abroad on an excursion with the company. In the late 1840's, O'Shaughnessy instilled *cannabis* into his practices as an anti-inflammatory, antispasmodic, anticonvulsant, analgesic, and a sedative[44].

As *cannabis* spread throughout the world, from Asia to the West, it encountered almost every culture[56]. Further historical and archeological accounts of *cannabis* in places such as Brazil, Jamaica, India, South Africa, Colombia, Ethiopia and Amsterdam are also available for research.

MARIJUANA IN AMERICA

Colonial *Cannabis*

Cannabis first touched American soil in the 16th century when the initial colonies brought plants from Europe to the New World. Hemp produced from *cannabis* plants were a vital tool for emerging colonies as they struggled to survive in the unfamiliar land. The extracted hemp was used to make rope, cloth and paper. The various applications using hemp from *cannabis* compelled the leaders of the first colony in Jamestown, Virginia to pass a law requiring hemp to be grown on every farm in 1619. In addition to this law, hemp was allowed to be exchanged as legal currency in Virginia, Pennsylvania, and Maryland[10] .

During the 19th century, marijuana plantations in Mississippi, Georgia, California, Nebraska, and New York thrived. However, hemp harvesting was heavily labor intensive. It had to be processed by hand, forcing the procedure to be time consuming and costly. After the Civil War, newly developed products and imported goods slowly replaced the role of hemp and the plant fell out of popularity. In addition, the invention of the cotton gin during the Industrial Revolution completely overshadowed hemp and it failed to compete[57]. *Cannabis* regained recognition between the years 1850-1937 as it was used as a medicinal drug and was openly sold in pharmacies and general stores. In 1906, the Pure Food and Drug Act required labeling of any remedies containing *cannabis*[5].

Mexican "Marijuana"

The Mexican Revolution in 1910 sparked an influx of Mexican immigrants into the United States. Between the years 1910-1930, more than half a million immigrants migrated from Mexico into America. War refugees and political exiles fled Mexico to escape the violence, bringing the habit of smoking *cannabis* with them. These immigrants called *cannabis* "marihuana" and for the first time, recreational *cannabis* use was being exercised in the American culture. Simultaneously, the temperance movements against alcohol instilled the

Volstead Act of 1920 which implemented the prohibition of production and distribution of alcoholic beverages. As alcohol became a pricey privilege, *cannabis* or "marihuana", rapidly became an attractive substitute and lead to increased use in the drug. Racists and anti-drug advocates associated *cannabis* with the unwanted, foreign citizens and campaigned against recreational *cannabis*; subsequently creating a negative stigma about *cannabis* to the public and lawmakers[10].

Although *cannabis* was not regarded as a consequential-major drug, several states banned the use of *cannabis* by the 1930's. Claims were being made that *cannabis* caused men of color to become violent and solicit white women for sex[10]. Seven years later, the Marihuana Tax Act of 1973 officially banned the use and sale of *cannabis*. In addition, the importation and cultivation were also heavily regulated. Importers had to endure a tedious clearance check along with paying a gruesome tax. Violation of the Act resulted in a $2,000 fine and imprisonment up to five years[10]. Scientific research on the medicinal properties and health benefits on the plant were halted as well.

Hippies

In the 60's and 70's, *cannabis* was a popular activity for activist groups fighting for rights and rejecting mainstream society. The term "dirty hippie" became associated with these individuals. The Marihuana Tax Act of 1937 was replaced by the Controlled Substance Act. This act established "schedules" for ranking substances according to their "dangerousness and potential for addition"[14] and federally outlawed marijuana. President Nixon agreed to label *cannabis* as a Schedule 1 drug, the same category as heroin, LSD and ecstasy. Schedule 1 drugs, "have a high potential for abuse and the potential to create severe psychological and or/ physical dependence...with no currently accepted medical use…"[14]. *Cannabis* was termed medically

useless and research was restricted. This designation made it nearly impossible for any physician or scientist to conduct *cannabis* research and it solidified that *cannabis* would not be developed for medicinal use.

Modern *Cannabis*

Despite the recent classification of *cannabis*, California was the first state to legalize the medical use of *cannabis*. In 1996, it became legal to be administered as medicine for patients with cancer, AIDS, and other painful illnesses[27]. In addition, multiple journals and newspaper articles where petitioning for a rescheduling of *cannabis* from a Schedule 1 drug due to its medicinal properties. Simultaneously, former presidents Gerald Ford, Jimmy Carter and George Bush were urging voters to reject the medical marijuana initiatives and in 1997, the National Institute of Health stated that there is insufficient scientific evidence to "…definitively asses marijuana's therapeutic potential…" They advised that the "…traditional scientific processes should be allowed to evaluate the drug's use for certain disorders."[20] However, in 1998, Alaska, Oregon and Washington all legalized medical *cannabis*, removing the state-level criminal penalties on the possession, use and cultivation of *cannabis* for patients with prescriptions[46].

Vermont and the state of Washington were the first states to legalize recreational *cannabis* in 2012 with Colorado following soon after[46]. Today, *cannabis* has made astonishing advances with it being legal in some form in over thirty states in America. In addition, two cannabinoid-containing medications have been federally approved. *Cannabis* popularity continues to increase as activists push for the reconsideration of its scheduling and its legalization. However, research is still hindered due to the current classification and federal stature of *cannabis*, forcing the knowledge of its health potential to remain unknown.

WHAT IS *CANNABIS*?

Botanical Description

To introduce the controversial plant, it is important to paint an image of the *cannabis* plant. The anatomy of the *cannabis* plant, also known as hemp, is comprised of several structures. *Cannabis* grows long-skinny, green stems with the large, iconic fan leaves extending from its nodes. The *cannabis* plant can be distinguished as male, female or sometimes both. Female plants produce large, colorful flowers that can be trimmed down to reveal round or pointed buds. Male *cannabis* plants produce small pollen sacs near the base of the leaves. These pollen sacs, like most plant species, allow the male plant to pollinate the female plant, subsequently triggering the plant's seed production. However, it is the seedless females, called sinsemilla, that are of interest for most *cannabis* cultivators because the flowers produced by a sinsemilla grow cannabinoid-rich buds. These buds are commonly used to unlock the psychoactive effects of the plant, and when people "smoke weed", this is what they are ingesting. When a plant is both male and female, it is called hermaphroditic. Hermaphroditic plants possess the sex organs of both a female and male, allowing the plant to pollinate itself during its own flowering.

The *cannabis* plant emerged almost 27.8 million years ago from *Humulus*, a plant genus responsible in giving beer its floral and bitter flavors. Both plants, *cannabis* and *Humulus*, make up the *Cannabaceae* family along with six other genera. However, when focusing on the genus *Cannabis*, there is no consensus on the taxonomy. For centuries, the taxonomy of *cannabis* at the species level has always been obscure. As a result of rising popularity, its taxonomy has become a more prevalent contentious issue. The "promiscuity" of the plant has blurred lineages boundaries[36]. The *cannabis* plant is capable of breeding with plants within its genus and can produce viable, complex offspring as a result. In addition, human cultivation and the cross

breading of naturally-wild *cannabis* plants with human-refined *cannabis* plants throughout the centuries has led its characterization to be a difficult task. However, categorization can still be attempted by examining the genotype (genetic makeup) and phenotype (physical traits) of a *cannabis* plant[36]. Some botanists argue there are three separate species of *cannabis*: *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis,* while other botanists believe that *C. indica* and *C. ruderalis* are simply subspecies of their mother plant, *C. sativa.*

Although it is unknown how and when the varying species of *cannabis* deviated and became separate entities, it is theorized to be from natural selection and where the seeds where farmed. It is certain that the environment altered the physical features of *cannabis*, leading to a new generation of *cannabis* plants and a diverse genus[54]. *C. sativa* is believed to originate from equatorial countries. The consistent year-round sun fostered taller and looser plants with finger-like leaves compared to its counterparts. *C. indica* is generally short and stocky in stature with wider leaves. Native to sub-tropical countries, such as Pakistan and Afghanistan, *C. indica* dedicated all its energy to flowering when furnished with an adequate sun season. The combination of fast germination and flowering along with its small radius –which permits for a higher ratio of plants to useable space—has made *C. indica* idea for farmers and growers today. Lastly, the *cannabis* plant believed to have engendered from central Asia and Russia is called *C. ruderalis*. This species (or termed sub-species), was forced to adjust to the harsh climates and shorter viable-developing seasons. It is the shortest of the three, growing to one to two feet. Unlike the other species (or termed sub-species), the flowering cycle of *C. ruderalis* is auto-flowering—meaning it is provoked by maturity. *C. indica* and *C. sativa* flowering is induced by light.

The morphological differences in branching, habitus, flowers and leaflets uncouples *C. indica* from *C. sativa* (see Appendix A) and *C. ruderalis* plants from the foremost. However, due to divergence from a common ancestor, *C. indica*, *C. ruderalis* and *C. sativa* nevertheless share similar characteristics, despite their dissimilar features.

Hemp

Hemp, as mentioned before, is the substance extracted from the fibrous stalks of *cannabis* plants. When comparing the genus, *C. sativa* tends to be more fibrous than *C. indica*. Scientifically, hemp is the vernacular used to describe varieties and biotypes of the *C. sativa* plant that contain less than 0.3% delta-9 tetrahydrocannabinol, or commonly known as THC[62]. For centuries, the fibrous qualities of hemp were utilized in fabrics, textiles, yarns, paper and fish-nets for ancient civilizations. These strong fibers were long and water-resistant.

Understanding Cannabinoids

Cannabis plants contain more than five-hundred chemical compounds; cannabinoids, terpenes and phenolic compounds[15]. Terpenes are the aromatic oils that categorize *cannabis* varieties with distinctive flavors like citrus or berry. Terpenes naturally develop on the plant to ward off predators and entice pollinators. Their development can be altered by the plant's surrounding environment, such as the climate, soil or fertilizer used. This characteristic allows for cultivators to shape and create different strands. Today, terpenes are very diverse. There are over one-hundred identified terpenes, ranging from cheese-smelling to floral. The most common terpenes are α-pinene and Myrcene (Appendix B). Terpenes are more impressive due to the ability to interact with other chemical parts of the plants.

The other chemical compounds in *cannabis* are called cannabinoids. These compounds are generally the target of scientific research, as they have seemed to offer potential health

benefits when unlocked. Cannabinoids naturally occur in the flower's resin of *cannabis* plants, but today, they can be produced synthetically in the lab. They are fatty components and there are over one-hundred and thirteen identified cannabinoids that are separated into three classes: endocannabinoids, synthetic cannabinoids, and phytocannabinoids. There are many different phytocannabinoids, with the most commonly known ones being delta-9-tetrahydrocannabinol (THC), CBD, tetrahydrocannabinolic acid A (THCA), and cannabidolic acid (CBDA)[15]. THC is responsible for the psychotropic properties of *cannabis* while CBD is non-intoxicating and generally known for the therapeutic benefits of *cannabis*. Strains of *cannabis* can now be cultivated and grown to obtain desired ratios of cannabinoids, such as THC and CBD. Strains can be high in THC with a lower concentration of CBD or vice versa. High CBD strains generally do not have high euphoric properties and deliver clear-headed functional effects instead. The strains that contain high levels of THC can cause people to experience anxiety, paranoia and dizziness. THC is most liable for the negative connotations that *cannabis* receives from the public.

Endocannabinoid System

Cannabis would have little to no effect on the human body if it did contain a biological system capable of interreacting with the cannabinoids in *cannabis*. This biological system is called the Endocannabinoid System (ECS) and it is a part of the nervous system. It is the main component in regulating the body's homeostasis or maintaining steady internal conditions. Cannabinoid receptors, endocannabinoids and metabolic enzymes are the three components that make up the ECS. The cannabinoid receptors belong to the G-protein coupled receptor family (GPCRs)[3]. They reside on the surface of cells, transmit information from the brain to the body and are responsible for eliciting appropriate cellular responses. Over the years of research, only

two cannabinoid receptors have been identified and accepted: CB1 and CB2[65]. CB1 is predominantly present in brain and spinal cord and it is one of the most abundant receptors in the brain. This receptor specifically regulates functions when the body is under the influence of *cannabis*. It regulates sleep, appetite, time perception and coordination[24]. The other receptor, CB2, are most abundant outside the nervous system, such as on cells in the immune system. This receptor regulates pain, inflammation and tissue damage[63].

Humans produce endogenous cannabinoids called endocannabinoids. Endocannabinoids are molecules that bind to the cannabinoid receptors and activate them, eliciting intracellular signaling[2]. Unlike cannabinoids in *cannabis*, endocannabinoids are produced naturally by the cells in the human body. There are also two major endocannabinoids: anandamide and 2-arachidonylglycerol (2-AG). They have been identified as having a role in pain modulation, control of movement, feeding behavior, mood, bone growth, inflammation and memory[11]. From what we know about the endocannabinoid system, it has been suggested that the chemical compounds of *cannabis* react with these specific endocannabinoid receptors throughout the human body and produce pharmalogic effects in the nervous and immune system.

MARIJUANA AS MEDICINE

Medical *cannabis* refers to the use of *cannabis*, specifically the cannabinoids due to their interactions with the human body, as a medical therapy to treat both physical and mental health aliments. Medicinal *cannabis* is administered with the intention of alleviating pain caused by diseases and illnesses such as: multiple sclerosis (MS), depression, anxiety, HIV, nausea and vomiting associated with chemotherapy, PTSD, epilepsy or opioid addiction[37]. Currently, there is enough substantial evidence to conclude that when administered, *cannabis* can help the treatment of chronic pain, nausea and vomiting associated with chemotherapy, and it can relieve the

spasticity episodes associated with multiple sclerosis. There is limited evidence that suggests *cannabis* can help with improving individuals' sleep patterns in illnesses such as sleep apnea or fibromyalgia that can negatively affect their quality of sleep. There is not enough evidence available to prove that *cannabis* has any ability to increase appetite or treat weight loss associated with HIV/AIDS, improve Tourette episodes, improve the anxiety of social anxiety disorders, nor the ability to improve symptoms of posttraumatic stress disorders. The call for clinical trials to observe these outcomes are necessary in order to determine conclusions regarding the desired subjects[42].

The limited clinical evidence that is available suggests that CBD specifically has various medical benefits. It can be used to help people with appetite loss from cancer or HIV, chronic pain, epilepsy, inflammation, sleep disorders, symptoms from MS, Crohn's disease, and is currently being tested in more debilitating diseases[12]. CBD has especially become popular because it has no lethal dose or any known serious medical side effects. CBD dosages, recommended by the Mayo Clinic, are based on the available scientific research, including publications and expert opinions[12]. For example, cancer patient that experience loss of appetite are prescribed two and half milligrams of THC to be administered orally accompanied with one milligram of CBD oil for six weeks. Patients with chronic pain are recommended anywhere from two to twenty milligrams of oral CBD while patients with sleep disorders are recommended anywhere up to one-hundred milligrams[12]. MS patients use an oral, *cannabis*-based spray containing anywhere from two milligrams to one-hundred and twenty milligrams of a THC/CBD complex. This spray is recommended to be used forty-eight times a day for fifteen weeks[12]. However, dosages can fluctuate depending on the patient's tolerance and request.

However, the FDA has not approved *cannabis* as a safe and effective drug for any indication[20]. They have only approved one medication, Epidiolex which contains pure CBD to treat seizures associated with Lennox-Gastaut syndrome (pediatric epilepsy) and two drugs that contain synthetic versions of cannabinoids substances that are naturally occurring in *cannabis*. Despite *cannabis* being illegal at the federal level, many states have officially legalized *cannabis* for medicinal purposes allowing numerous doctors, researchers and patients to take advantage of it.

Qualifying for Medical Marijuana

For patients to be administered medical *cannabis* in a state where it is viable, they must first qualify for a medical marijuana card. In order to do so, patients must first meet with a certified doctor in order to have their condition(s) assessed. The certified doctor must diagnose the patient's aliment and determine if it is an ailment that is on their state's list of qualifying medical *cannabis* conditions. If so, the doctor recommends medical *cannabis* for the patient and completes a form for the patient. Once the patient gets approval from a certified doctor, they must then apply to their state or county's medical *cannabis* program. They must schedule an appointment and bring a completed application, government ID, proof of living, money for qualifying fees and the verified form from their physician[20]. Once they are accepted into their state or county's medical marijuana program, they are administered a medical marijuana card which authorizes the patient to visit dispensaries and purchase medical *cannabis* products. The card is valid for a year and the patient must reapply forty-five days prior to the card's expiration date by submitting to the previous process. Application requirements vary with each program.

Accessibility and qualifications for a medical marijuana card also vary state-to-state. In some states, only patients with serious and debilitating conditions are allowed access to medical

marijuana, such as Alabama, while other states have a long list of qualifying conditions, such as Alaska. Additionally, the availability of medical *cannabis* products varies as well. For example, in Ohio, it is illegal to smoke the *cannabis* flower itself; only concentrates, edibles, vaping and oils can be administered to patients that qualify for medicinal *cannabis*[43]. In Tennessee, the only legal medical *cannabis* product is CBD oil[32].

Cannabis and Epilepsy

As previously stated, clinical data and research has suggested that *cannabis* can help with various serious diseases and pain management. There is significant evidence demonstrating a positive relationship between *cannabis* and seizure disorders. One in every twenty-six Americans develop epilepsy within their lifetime and there are over 3.4 million people who suffer from the crippling disease[64]. Most forms of epilepsy cannot be treated with over the counter medications[15]. Therefore, it is common for most states to approve epilepsy and seizure disorders as qualifying conditions for medical *cannabis*. *Cannabis*, specifically CBD, is recognized for its anti-seizure properties and it has been shown to reduce the frequency of seizures[16]. Epidiolex was the first FDA-approved *cannabis*-based drug released to all fifty states in the United States to treat epileptic syndromes[16]. In order to use it, patients must be two-years old or older and have not had success with other treatment drugs in the past. Epidiolex is a clear, oral solution that contains 100 mg/mL of cannabidiol (CBD) concentrate. Patients start by taking an oral dose of 2.5 mg/kg Epidiolex twice a day. After one week, the dosage is increased to 5 mg/kg twice daily. Furthermore, dosages can be changed based on the individual's response and tolerability[16]. Like most antiepileptic drugs, including Epidiolex, data suggests that patients should stop usage if they experience sedation, suicidal behavior, or any other adverse health effects. However, while

Epidiolex is FDA-approved and classified as a Schedule V substance, *cannabis* and CBD remain in Schedule I.

In 2013, an eight-year-old girl from Colorado, named Charlotte Figi, was treated with medical *cannabis* in order to alleviate her rare and debilitating Dravet syndrome. Charlotte's form of epilepsy was unable to be treated with other medications, but she found that *cannabis* significantly reduced her seizures. Charlette's public story sparked scientific research to provide considerable evidence that *cannabis* could be an effective, alternate medication for treating epilepsy. In 2016, *The Lancet Neurology journal* released an article confirming that cannabidiol has the potential to reduce seizure frequency and "…might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy."[15] The article also pressed the need for further investigations to be conducted. Additionally, in another case study, various parents of children with some form of epilepsy were surveyed about their opinion on the use of cannabidiol-enriched *cannabis* as a treatment plan[45]. Eighty-four percent of parents reported that their child's seizure frequency reduced when taking cannabidiol. Eleven percent of these parents reported complete seizure freedom[45]. The parents also reported that their child experienced increased alertness, better moods, and sleep improvement. However, like most clinical data published research, it concluded with, "safety and tolerability data for cannabidiol-enriched *cannabis* use among children are not available. Objective measurements of a standardized preparation of pure cannabidiol are needed to determine whether it is safe, well tolerated, and efficacious at controlling seizures in this pediatric population with difficult-to-treat seizures."[45]

***Cannabis* and Cancer**

Medicinal *cannabis* is also often used to treat cancer patients in hopes to help alleviate the horrible side effects of the disease[2]. Chemotherapy-induced nausea, inflammation, loss of

appetite and general pain can be treated with the help of *cannabis*. The licensed and FDA-approved drugs, dronabinol and nabilone, can be administered to treat such side effects. Dronabinol is a synthetically-produced delta-9-THC while nabilone is a synthetic derivative of delta-9-THC. These medications are typically prescribed to cancer patients who have not had success with previous treatment drugs for chemotherapy side-effects. The recommended dosage of nabilone is determined based on the patient. However, the common dose of is one to two milligrams orally taken twice a day. When the body is getting use to the drug, it is common for patients to experience dizziness, fog-brain and headaches[2]. Dronabinol is a liquid medication also taken orally up to four to six times a day, once again, based on the patient's tolerance to the drug. However, dronabinol can be addictive. If patients stop the use of dronabinol, the possibility of withdrawal symptoms, such as trouble sleeping or irritability, can be seen[2].

It has been proven by various clinical studies that THC is an effective antiemetic—a drug effective against vomiting and nausea. In a study conducted in 1980, it was concluded that THC was an effective antiemetic in many cancer patients that were receiving chemotherapy in addition to patients for which other antiemetics were ineffective[31]. THC proved to be more effective in treating vomiting and nausea compared to both the placebo and another treatment drug, prochlorperazine, in a "randomized, double-blind, crossover trial with patients who had failed to benefit from standard antiemetic therapy"[51]. These test patients also preferred THC over placebo and prochlorperazine. In 2014, a poll from WebMD expressed that eighty-two percent of oncologist believed that patients should have access to *cannabis*[2]. In addition to pain management from side effects of cancer, it has recently been under question if *cannabis* influences shrinking tumors or slowing cancer growth. In a scientific article titled, "A pilot clinical study of delta-9-tetrahydrocannabinol in patients with recurrent glioblastoma

multiforme", suggested that THC inhibited tumor-cell proliferation *in vitro* and decreased tumor cell Ki67 (cancerous) when immunostaining[26]. However, due to research restrictions, only a total of nine individuals were tested. The study also concluded that THC is most likely not the best cannabinoid to use for antitumoral studies. There are countless studies available that discuss the progression of *cannabis* associated cancer repercussions, however, the *cannabis* prohibition at the federal level continues to delay further investigation and evidence. There is not enough research to convince oncologists to recommend the herbal plant over medications that they have seen work, possibly withholding relief from thousands of patients[26]. *Seattle Cancer Alliance* completed a cross-sectional survey of cancer patients in the Washington area and found that seventy-four percent of the examined patients stated that they wanted to know more information about *cannabis* and its uses from their cancer team but only fifteen percent reported receiving information from their physicians[11].

Cannabis and Multiple Sclerosis

Some of the strongest advocates for the *cannabis* movement are patients with multiple sclerosis. Multiple sclerosis (MS) is a disabling disease of the central nervous system that disrupts the flow of information from the brain to the rest of the body. *Cannabis* helps treat common symptoms such as pain, inflammation, muscle spasms, abdominal discomfort and depression. The recent research conducted on MS and *cannabis* has suggested that *cannabis* helps mediate the pathogenetic mechanisms and symptoms of related to MS. The American Academy of Neurology conducted a study in 2014 that concluded that an oral *cannabis* spray was most effective in treating these symptoms when compared to nabiximols or synthetic THC[44]. The oral spray was more effective in improving spasticity and pain. Synthetic THC and smoked *cannabis* did not produce enough evidence to determine the effectiveness of each[44]. In addition,

they discovered that both the oral spray and synthetic THC were effective in reducing the amount of bladder voids per day. However, neither THC nor oral *cannabis* proved to be effective for tremors[44]. Additionally, strains that contain higher ratios of CBD relative to THC have positive effects on muscle spasticity and pain caused my MS[50]. However, there is not enough information available from clinical research trials to truly decipher the effectiveness on *cannabis* with MS.

Cannabis and Mental Illness

The relationship between *cannabis* and mental illnesses can be complex. Many believe that *cannabis* induces mental illnesses such as anxiety, depression or suicidal-behavior while others argue *cannabis* improves mental illness symptoms. However, there is not enough supporting evidence on either side due to the lack of research. Generally, the only trials completed on *cannabis* and mental illness is obtained through the general public, when *cannabis* users self-administer outside of a laboratory setting or with a medical recommendation of *cannabis* through a physician in a medical *cannabis* program.

The National Institute of Mental Health has stated that eighteen percent of Americans eighteen and older are affected by anxiety disorders[7]. Since the endocannabinoid system is believed to be responsible for regulating moods and eradicating aversive memories, many have made *cannabis* a popular alternative to prescription medications to treat anxiety-related symptoms. Preclinical evidence suggest that CBD can effectively treat anxiety-related disorders when orally administered at dosages ranging from fifteen to sixty milligrams[7]. Additionally, Emily O'Brien is the founder of Mondo, a company that sells a *cannabis*-based powder to treat anxiety symptoms. This powder allows victims of anxiety to obtain relief through micro-dosing *cannabis*. Patients are able to precisely measure the amount of THC to the milligram so that they

can obtain the therapeutic effects of *cannabis* without reducing their mental dexterity. O'Brien believes the microdosing of *cannabis* is a technique that will be implemented in the future of prescription-drug replacement because it is relief without intoxication and chemicals[35]. Microdosing or acute dosages of *cannabis* and CBD have the potential to become a treatment for anxiety disorders, but, due to the lack of research and understanding on cannabinoid mechanisms and the relationship between *cannabis* and anxiety, it remains questionable.

Cannabis has also become in question for its ability to treat physiological illnesses, such as depression. The current American treatment of this illness includes prescription antidepressants. However, antidepressants can take weeks to take effect and patients can experience additional adverse side effects. When compared to these drugs, *cannabis* works fast to stimulate the endocannabinoid system and has little side effects. A study conducted by McGill University found that high dosages of THC worsened depressions symptoms while low dosages of THC produced serotonin in the brain, helping relieve depression symptoms[33]. This is one of the first studies to conducted on *cannabis* and depression and provide evidential research confirming *cannabis* can positively affect people suffering from depression or symptoms of depression. Besides this study, there is little evidence that *cannabis* or derivatives of *cannabis* can be effective in reducing depressive symptoms[33]. The lack of research on *cannabis* and depression also creates a deficient amount of research on the role of *cannabis* with suicidal behaviors. If *cannabis* were known to cure or treat depression, it could then be used to help reverse suicidal behavior. Proponents of utilizing *cannabis* to battle depressive thoughts claim that *cannabis* helps them battle life stressors and allows them to see things in a positive light[31]. Yet, once again, there is a lack of scientific trials and evidence on this topic.

Cannabis **and Opioid Addiction**

One of the leading causes of accidental death in the United States are from prescription drug overdoses. According to the NIH, more than one-hundred people die each day from overdoses in the United States[49]. This serious national crisis has demanded attention and interventions. In attempts to decrease the amount of opioid related deaths, many have turned to the idea of substituting prescription drugs for *cannabis* or administering *cannabis* alongside opioid usage. When opioid-users also used *cannabis* either through edibles, vapors or smoking, their opioid use reduced by forty to sixty percent[8]. Some also admitted that they preferred *cannabis* instead of their prescribed drugs. *Cannabis* can be a safe, effective and non-addictive alternative medicine and the effectiveness of *cannabis* in pain management and tolerance has been proven in previous trials.

Additionally, the endocannabinoid system and the opioidergic system share similarities within the human body, making *cannabis* an impactful alternative to opioids[65]. Cannabinoids in *cannabis* reacts with the endocannabinoid system CB1 receptors in order to help alleviate opioid withdrawal symptoms and opioid use. *Cannabis* also has the potential to prevent the chance of relapse and reduce the amount of opioid related deaths. However, due the federal barriers on *cannabis*, patients suffering from addictive opioid use are unable to obtain access to medical *cannabis*. There are thousands of people each day struggling with opioid addiction and unable to reap the possible benefits that *cannabis* can administer to addiction.

RESEARCH STRUGGLES

Despite the various experimental evidence and data on the effectiveness of *cannabis* on human health and the growing popularity of cannabis in the medical field, it remains a Schedule 1 drug. This classification has created significant obstacles to research and has hindered further understanding of *cannabis*. The federal barriers instilled for cannabis has made research on the

substance virtually impossible. In fact, scientists have a harder time accessing and creating research on *cannabis* than they do with any other illicit drug. The increasing patterns of *cannabis* use and support have demanded for more information on the drug's health effects, both negative and positive. Yet, the science community has failed to convince the federal government to reschedule the substance and federal research policies continue to block externally valid, randomized clinical trials on *cannabis*. Federal barriers including a lack of federal funding, a complex research approval process and a shortage of clinical *cannabis* necessary for conducting research, have all attributed to the hindrance of *cannabis* knowledge, potential and patient relief.

Administrative Barriers

Before scientists conduct research on cannabis or its cannabinoids, they must trek through a series of review processes with multiple federal agencies. The scientist, or his/her sponsor, must first obtain a pre-investigational new drug (IND) number by submitting an IND application to the Food and Drug Administration[21]. The IND is a request for the FDA to authorize the investigational drug to be administered to humans. The federal law requires a new drug to be approved for marketing before it is transported or distributed across state lines. However, when conducting research, the IND acts as an exemption from this rule so the investigational drug can be shipped from state to state during clinical trials[21].

In order for the FDA to accept the IND application, the sponsor or physician must prove that the drug passes various protocols and provide exclusive information within the application[22]. The IND application must contain the drug's animal pharmacology and toxicology studies, manufacturing information and clinical protocols and investigator information[22]. The sponsor or physician must have data confirming that the drug is reasonably safe for the initial testing in humans, manufacturing information that ensures the drug can be easily produced and

consistently supplied, detailed protocols regarding the clinical studies that were conducted to assess the risks of the drugs, information on the qualifications of the clinical professionals responsible for the trials, evidence of research subjects' consent, and a review of the study from an institutional review board[22]. All these components must be included to satisfy the FDA regulations. Once the IND is submitted, the physician or sponsor must wait thirty days before initiating research and beginning the clinical trials. If the FDA determines that the proposed research contains potential hazards for the research participants or that the IND is lacking in any way, the research will be put on hold until the sponsoring researchers resolve the highlighted issues[22]. The IND application process is tedious, and it forces researchers to follow a regulatory path, including continuous check-ins with the agency.

Supply Barriers

Researchers conducting clinical research on *cannabis* or cannabinoids must use federally approved *cannabis*. The research-grade *cannabis* for scientific study is supplied through the National Institute on Drug Abuse (NIDA) Drug Supply Program. The Drug Enforcement Administration (DEA) regulates *cannabis* cultivation for research purposes through license requirements and by "establishing annual aggregate production quotas under the authority of the 1970 Controlled Substance Act."[42] However, the DEA has only offered one license for the cultivation of *cannabis*. This license belongs to the University of Mississippi and since 1968, they have been the only facility allowed to provide *cannabis* for research[40]. The University of Mississippi has a designated plot of land, a twelve-acre farm, where *cannabis* is grown every few years, based on the demands of the substance. The *cannabis* is harvested and stored in their facilities as well, awaiting distribution[58].

In the past, the *cannabis* outsourced from the University have been few and limited. There was only a certain amount of varieties of the plant. The lacking variety of *cannabis* determined what could actually be researched. Other fields of interest that their *cannabis* did not pertain to were neglected. Additionally, the *cannabis* produced at the University is "manicured to a uniform particle size because it is required to be standardized in various research protocols."[58] Therefore, the potency of the *cannabis* grown at the University is weaker when compared to *cannabis* that can be purchased at legal dispensaries. This discrepancy in potency can have an obvious effect on researchers' experiments.

As mentioned before, the University grows *cannabis* in accordance to the rate of demand. Often times, the *cannabis* that is unused is confined to a freezer. It is known that the temperature at which *cannabis* is stored can also affect the potency and molecular components of *cannabis*[55]. Lower temperatures slow the process of decarboxylation of the cannabinoids, essentially degrading the desired amount of delta-9-tetrahydrocannabinol (THC), and subsequently affecting the quality[62]. If stored improperly, *cannabis* can also acquire mold and or yeast. As of now, it unclear how yeast and mold affect the plant. There is currently no established standard for accepted levels of mold or yeast on *cannabis* plants, which is quite concerning[63].

In order to obtain the desired *cannabis* for research, investigators must obtain an administrative letter of authorization (LOA) from the NIDA. This letter describes the manufacturer's facilities as well as the characteristics of the desired *cannabis* needed for the research. In addition, the DEA also requires researchers to apply for a DEA registration and site licensure in order to confirm that the *cannabis* they are supplied with is in fact for research purposes[4]. Due to the University being the sole facility to provide federally legal *cannabis* for research, it is no surprise that it cannot provide the array of products, potency nor the quantity as

numerous amounts of legal dispensaries[24] can. This monopoly creates a bottleneck and further delays in necessary research.

Funding Barriers

Funding for *cannabis* research is also an obstacle for researchers. Due to the scheduling of *cannabis*, it is almost impossible for a researcher to receive any substantial amount of federal funding. Currently, the NIDA is responsible for funding research for multiple health domains, including *cannabis* research[39]. However, the NIDA does not pursue or support research regarding the potential therapeutic or health benefits of *cannabis*. Instead, the goal of NIDA is to "advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health"[41]. Therefore, it is even harder for researchers to obtain federal funding on topics that combat the NIDA's mission. Additionally, the lack of federal funding puts research at a disadvantage. Researchers are unable to keep up with the ever-changing pace of the *cannabis* world, causing a bigger gap in understanding the comprehensive health effects of *cannabis*. Without respectable financial support, the necessary research to convince physicians, health professionals and law-makers is scarce and underwhelming.

Achieving the Perfect Dose

Personalized medication in healthcare is tailed to an individual's clinical, genetic and environmental information. Successful personalized medicine is generally difficult to achieve due to the complexity of every individual's internal matrix. Doctors and patients often struggle when finding the perfect balance of *cannabis* to administer at times due to the absence of education on the substance. Yet, this can be combatted by the various applications available for patients to experience the medical benefits. Patients have the opportunity strategize with their

professional healthcare provider to design a treatment plan most suited to their individual desires and concerns. This flexibility has made *cannabis* a more popular alternative medication. A patient can decide for themselves the type of *cannabis*, the type of product and the potency of *cannabis* that would be best suited for them, with the help of doctor recommendations. Oil concentrates, non-intoxicating products containing high traces of CBD (five to twenty percent) instead of THC and vaporized-smokeless delivery systems have helped transform the view of therapeutic *cannabis*[11].

However, due to the lack of science and clinical-trial evidence on *cannabis*, doctors and patients are realistically underqualified to determine the adequate dosage, type of delivery, and the potency of *cannabis*. Generally, dosages are determined by the physician and altered base on the patient's reactions and tolerance. Most graduated doctors and medical physicians were not introduced to *cannabis* during their medical education; therefore, most are inexpert to counsel patients on correct dosages and different administrations. Over eighty percent of recent medical school graduates did not receive any education on *cannabis* throughout their studies, training, residencies or fellowships[37].

In most of the previous trials conducted, CBD and THC were administered by smoking or by an oral medication. Smoking is generally effective because the lungs are efficient in delivering necessary drugs into the body and it allows the cannabinoids to be administered into the human blood steam instantaneously. CBD medication can also be delivered orally by using an oil-based capsule[3] or an oral spray as mentioned previously. Oral administration is effective because it forces the substance to pass through the liver, where it can be easily broken down and metabolized. The limited research has already demonstrated evidence proving the medical value of *cannabis*. Once the barriers to *cannabis* research are lowered, scientists and pharmaceutical

companies will turn their interest and efforts into discovering how to administer the drug in order to optimize the therapeutic benefits and achieve the highest relief possible for patients.

Current Consensus

Cannabis is widely used around the world, from adolescence to the elderly. In the United States alone, the recreational or medicinal use of *cannabis* is slowly becoming more popular and considered less of an abhorrence. In 2015, it was estimated that twenty-two million Americans used *cannabis* each month[37]. Additionally, the same survey conveyed that *cannabis* usage is more prevalent among men than women. Appendix E depicts *cannabis* usage distributed based on demographics in 2015. Today, in states which recognize the medical purposes of *cannabis*, there are more than three-million legal medical marijuana users. Additionally, sixty-two percent of Americans support the legalization of *cannabis,* according a survey conducted by the Pew Research Center[28]. Polls also show that American Democrats support the legalization more so than Republicans[28]. As the public support and state legality of *cannabis* continue to grow, it is expected that the percentage of *cannabis* acceptance will grow subsequently. There are eleven U.S. states where *cannabis* is currently fully legal: Washington, Vermont, Oregon, Nevada, Michigan, Massachusetts, Maine, District of Columbia, Colorado, California and Alaska with medicinal *cannabis* legal in thirty-five states.

Additionally, many states have decriminalized *cannabis* or have reduced their laws to lower the repercussions of possessing, using or distributing the substance. However, it is a continuous battle between federal *cannabis* laws and state laws, creating challenges and confusion how where the line is drawn. Even if *cannabis* is legal in the state you live in, there are federal regulations that still apply. *Cannabis* cannot be on the premises of federal land such as national parks, military bases or ski slopes[23]. Federal employees are not allowed to use *cannabis*.

Students whom receive federal financial aid could lose their funding if they are affiliated with *cannabis* as well as people who live in federally subsidized housing. Additionally, *cannabis* users can be rejected from purchasing a firearm due to the federal regulations on *cannabis*. The failure to comply with federal regulations of *cannabis* can still face detrimental repercussions[23].

FUTURE OF *CANNABIS*

Unfortunately, to this date, the medical use of *cannabis* remains controversial in the United States. Despite the research evidence available from case studies, personal accounts and observations, there is not enough high-impact clinical evidence accepted by the FDA. Therefore, *cannabis* continues to be federally outlawed and deemed a Schedule 1 drug, the highest level of prohibition for a substance. In addition, there is currently no accepted medical use of *cannabis* by the FDA, therefore, it will continue to be unapproved by the FDA until that is accomplished. Federal restrictions limit the necessary research and evidence, further creating a barrier to our understanding of the potential benefits and risks that *cannabis* has to offer.

The basic and clinical research on *cannabis* that is legal today is expensive as well as exceedingly and unnecessarily difficult to conduct. The federal barriers instilled on *cannabis* hinders the advancement of knowledge on the substance, causing for the therapeutic effects and health risks associated with *cannabis* to remain unknown. With wide-spread state legalization under consideration, a demand for appropriate research and knowledge is important now more than ever. Federal barriers need to be reviewed and lowered in order for clean *cannabis* to be more accessible for research and for us to finally fill the void of what we don't know about *cannabis* benefits and harms. Until then, *cannabis* research and federal agencies remain in a 'Catch-22' scenario.

People are still pushing for progression in *cannabis* research because of all of the uncertainties. There are numerous components to *cannabis* that we still do not understand. The complete mechanisms of *cannabis* are not completely understood and there are hundreds of cannabinoids that are still unknown to science. We do not know how many exact cannabinoids there are, and we do not know what a lot of them do. There could be hidden cannabinoids that possess greater health and therapeutic benefits that are waiting to be discovered.

Without this knowledge, we are unable to fully grasp the implication and benefits *cannabis* when interacting with the human body. There is very limited evidence that supports or opposes the effects of *cannabis* with depression, anxiety, epilepsy and MS. Additionally, preliminary studies on *cannabis* with cancer cells, pregnancy, diabetes, and heart health are also necessary but cannot be completed due to the mentioned federal barriers. Other issues of incomplete *cannabis* research are that are unable to understand the correct dosages of *cannabis*. Personalized *cannabis* treatment is currently unobtainable. Therefore, patients are withheld from possibly achieving the optimal relief from *cannabis*. If *cannabis* were to be understood at a higher level, personalized strains with desired ratios of THC and CBD (or other cannabinoids) could be achieved.

In addition, it is important to recognize that the previous work completed in clinical trials and evidence were completed following federally recognized regulations. All of the *cannabis* research completed thus far has been conducted using one single source of *cannabis*, from the NIDA's supply at the University of Mississippi. This *cannabis* is known to be low in potency and quality, causing the resultant research to contain possible errors and the possibility to have little validity in modern day *cannabis* life.

The overall gaps in our knowledge on *cannabis* dosages, cannabinoid content and ratios, contradictions, misuse liability, effectiveness of different administrations, cannabinoid mechanisms, cannabinoids, bioavailability and many other unanswered questions continue to stimulate a negative stigma towards *cannabis*. The federal government and agencies also promote this negative stigma of *cannabis* by rejecting any information from trials that were not federally-approved and withhold publishing medical benefits of *cannabis* to the general public. The federal labeling of *cannabis*, funding barriers, and lack of access to real-life *cannabis* in clinical research and studies contribute our inability to fill the void in our comprehension on *cannabis*. As *cannabis* use becomes more prevalent, it is imperative that we understand how it can impact our bodies and our society.

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Appendix

Appendix A:

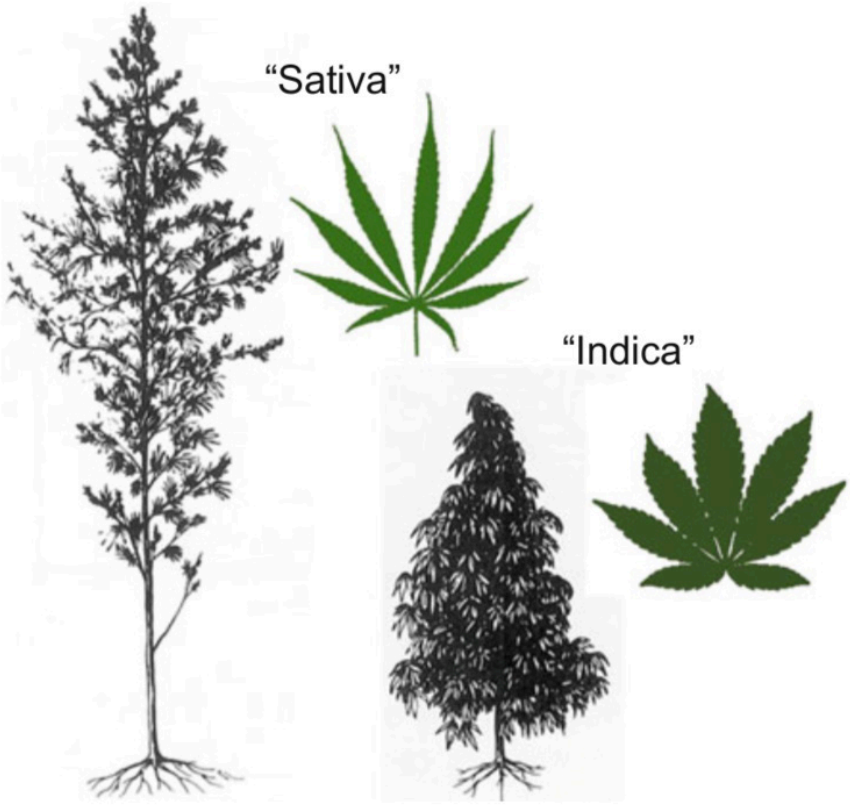

Figure 1: Visual difference in morphological features between *C. sativa* and *c. indica*.

Appendix B:

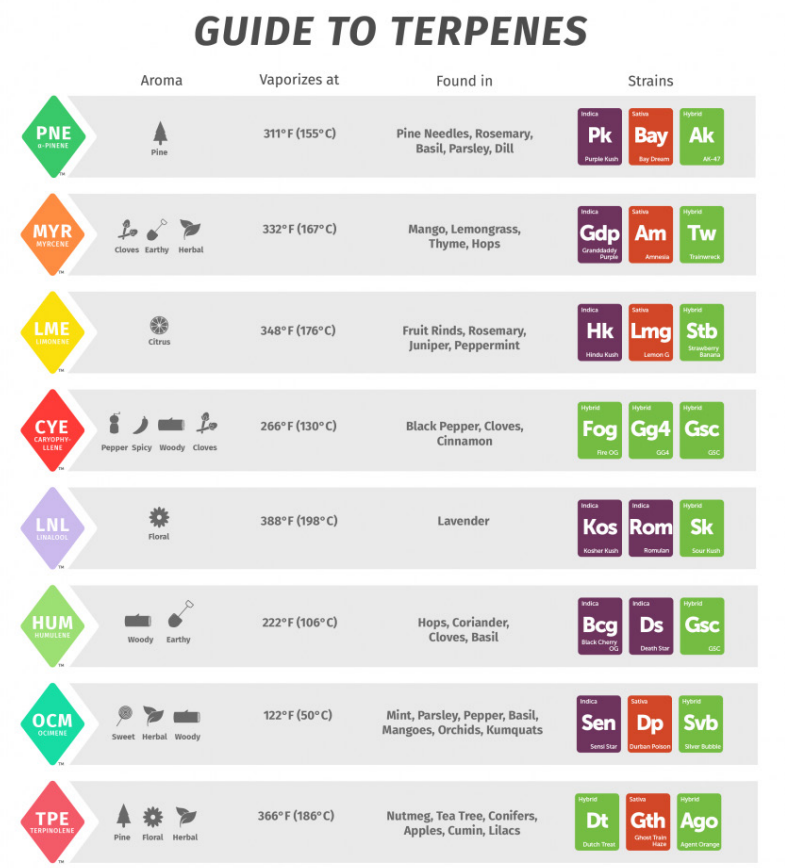

Figure 2: This table serves as a guide for the eight, most common terpenes found in *cannabis*.

Appendix C:

Step 1: Sponsor obtains a pre-IND number from the FDA.

Step 2: Sponsor contacts NIDA or another DEA-registered source of marijuana to obtain information on the specific strains of marijuana available, so that all necessary chemistry, manufacturing, and controls (CMC) information can be included in the IND application.

Step 3: Sponsor contacts DEA for registration application and Schedule 1 license.

Step 4: If applicable, Sponsor obtains from NIDA as Letter of Authorization (LOA) to reference CMC information in NIDA's Drug Master File (DMF) on file with FDA.

Step 5: Sponsor sends copy of IND/protocol, including a LOA to reference CMC information in a Drug Master File (if applicable), to FDA and DEA.

Step 6: FDA reviews the IND.

Step 7: Sponsor contacts NIDA or another DEA-registered source to obtain the marijuana after the FDA completes its review of the IND, and the DEA registration is received.

Figure 3: This table summarizes the steps described on the U.S. federal Food and Drug Administration for the process required for any *cannabis* research.

Appendix D:

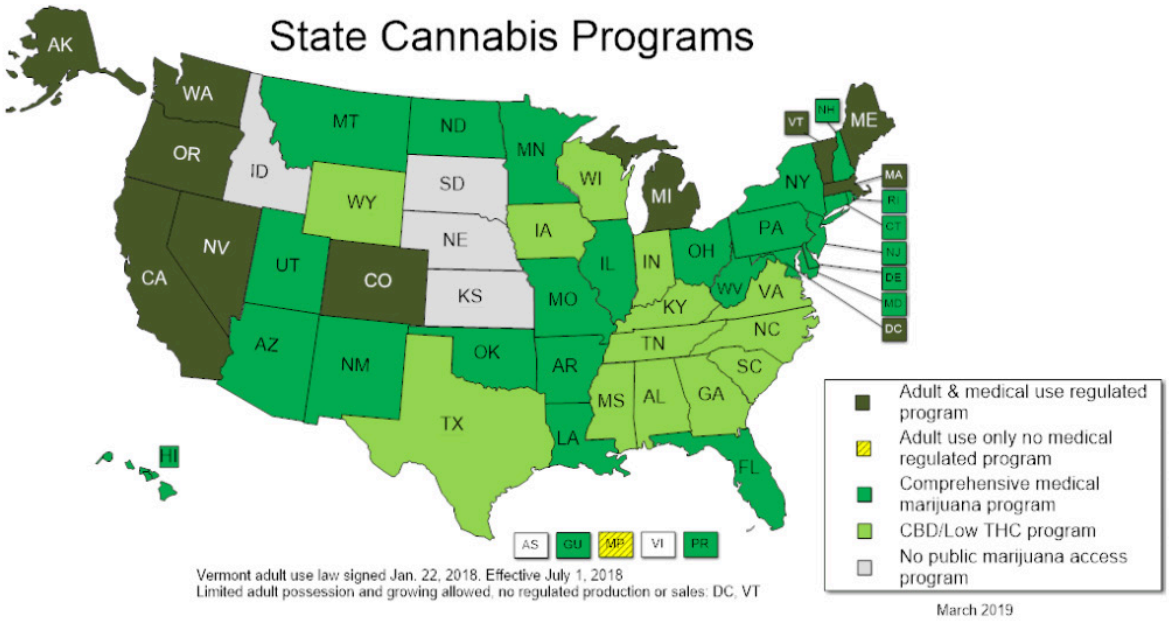

Figure 4: Depiction of the legality of *cannabis* in the United States.

Appendix E:

	Past-Month Use Rate (%)
Ethnicity	
White, Non-Hispanic	8.4
African American, Non-Hispanic	10.7
Hispanic	7.2
Asian Non-Hispanic	3.0
Gender	
Male	10.6
Female	6.2
Education	
Less Than High School	8.2
High School Graduate	9.1
Some College	10.5
College Grad	5.9
Family Income[a]	
Less than $10k	13.6
$20k–$29.9k	9.7
$50k–$74.9k	7.8
$75k +	6.6
Age[a]	
12–17	7.1
18–25	20.1
26–34	13.0
35–49	7.1
50+	3.9

Figure 5: Past-Month usage of *cannabis* by Demographic in 2015. Table taken from National Academies of Sciences.