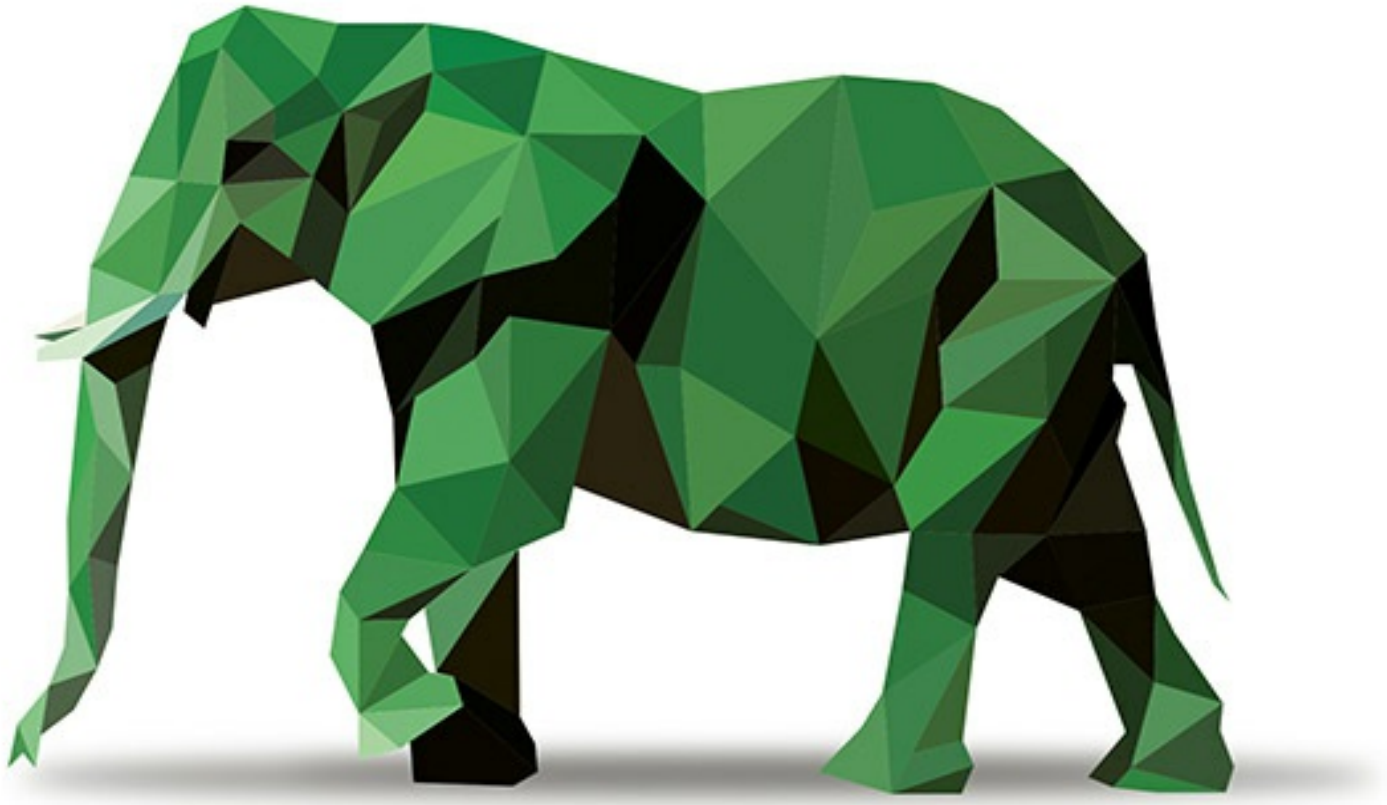
The GREEN ELEPHANT



THE HEALTHCARE PROVIDER'S ESSENTIAL GUIDE

TO UNDERSTANDING & ADDRESSING

MEDICAL CANNABIS & CBD

MATTHEW FOGEL, FNP • ELIZABETH FOGEL, FNP • JEAN-PAUL DEDAM, MD

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PREFACE

It can be quite intimidating for a medical practitioner to approach the area of cannabis. The information available—and the feelings surrounding it—seems to differ from person to person, even in the medical community, with some providers championing cannabis use and others demonizing it. But as with any new challenge in medicine, every promising therapy must be explored—and cannabis is no exception.

One of the key problems frustrating the debate around cannabis is that, up to this point, the discussion has been purely academic. Yet any provider who has practiced on their own knows that there is an enormous difference between "book practice" and "clinical practice." Book practice is the "perfect world" scenario, and is what makes providers believe that every patient who presents with "X disease" will present in exactly the same manner and needs to be treated the same way. In the real world, we know this to be far from the truth, with no two patients presenting exactly alike. In the same way, no two patients will respond to a given therapy in exactly the same manner.

In debating whether we as medical practitioners should or shouldn't use cannabis as a therapy, we have failed to appreciate that our patients live in the real world. They have *already* heard of the potential benefits of cannabis therapy from friends and neighbors, by looking online, and even in national news. Regardless of where any provider lands on the topic, they have a responsibility to consider that, given the current national shift in opinions about cannabis, their patients *are* going to try cannabis. Given this fact, it is our professional obligation to educate ourselves that we might better assist them in using cannabis in the safest manner possible, to help them with harm reduction.

But how best to go about educating ourselves? Some of the more commonly used arguments against cannabis therapy are, "We haven't researched it enough" and, "We just don't know much about it." And while there is some validity to both of these statements, the opposite is also true: despite many believing our knowledge of cannabis to be only very recently acquired, nothing could be further from the truth.

Cannabis therapy has been used for millennia and research into many of its potential benefits, such as neuroprotectant properties, isn't "just coming out"; it has been known about and researched since the 1800s. This is not new information, but rather information that was lost to us through the demonization and prohibition of cannabis, itself motivated by the unsavory factors of racism and greed. Yet despite this burying of information, the truth always comes to light; and now, with modern technology, we are rediscovering those things which were previously thought lost.

Then, there is the complaint that our current understanding of cannabis therapy does not conform to the modern standards of scientific rigor. There is currently an outcry from medical providers who cite the lack of double-blind studies on the subject, as though these are the only legitimate sources of clinical evidence. Patient reporting, while anecdotal, is one of the best current clinical guides for clinicians attempting to navigate cannabis therapy. These accounts come from patients who are experienced and know what works for them, so rather than upset the apple cart of effective therapy, we should listen to them.

The experienced user knows:

1) What they are looking to gain from therapy
2) The dosage that helps them to achieve that desired effect
3) How much will give therapeutic effect and still allow them to function throughout the day

How many patients taking other medications can actually give us this information? Experienced medical cannabis patients have a knowledge base about their medication that most patients do not possess.

The reason for this is two-fold. The first is the general lack of knowledge among healthcare providers about the medical effects of cannabis. Patients have to learn what to look for and what works, because the people who *should* be guiding the discussion—the medical community — do not have the necessary familiarity with the subject to do so. The second reason is the stigma that is still associated with cannabis use. To be able to use cannabis for medical purposes, patients have to educate themselves to be better able to defend that usage to family and friends and avoid demonization themselves.

When all is taken into consideration, a new light is cast on patients who medicate with cannabis. Exploring just what that light reveals is the

purpose of this book.

MY BACKGROUND

If you had asked me as a child what I wanted to be when I grew up, a nurse or a nurse practitioner would not have even cracked the top fifty. I was obsessed with basketball in my youth, certain that NBA stardom was only a few years away. I would practice for hours on end, long after dark.

Interestingly, this is when my first experiences with cannabis began. I grew up in a very conservative Christian household and received the traditional "drugs are bad" speech, but during my fourth-grade year, I began causing trouble as a way to cope with the loss of my grandfather. This continued into my fifth-grade year, with the trouble becoming worse and worse, until my parents removed me from school and started homeschooling me. However, rather than study, I spent much of my time in the driveway practicing my basketball skills.

Late one fall evening, some of my friends and former classmates came over to visit as 11-year-old me was home practicing basketball. One of them, whom we will call Joe, asked if he could smoke a cigarette. I told him that was fine, and both he and another of my friends began to share the "cigarette." About a minute after they began smoking, my dad came outside. He was smiling and about to say something when he smelled the smoke. Immediately, his whole demeanor changed. He became cold—not mad, but completely even-keeled, just taking care of business. He told me it was my bedtime (it wasn't) and that my friends needed to go home. After a brief goodbye, I was rushed into the house and subjected to a line of questioning that would shape my views on cannabis (and drugs in general) for the next 14 years.

He immediately asked if I had smoked any of their "cigarette," to which I responded with a resounding no. His tone softened, as he said, "They were smoking marijuana. I know the smell of it from the Army barracks. People used to smoke it and act like idiots."

I came away from this discussion with the understanding that not only would using marijuana kill my chances at playing basketball, it would make me stupid. I took this to heart; marijuana could ruin my mind, life, *and* the chance to play the sport that I loved. No thanks. These statements, along with many others across the years from many different sources, would shape much of my thinking on drug policy as I went into my career as a medical professional. Some statements came from friends and

colleagues, some from medical journals or news stories, but they held one thing in common: all were filled with mistruths, and many were outright lies. Still, the information was from sources I trusted, so I deemed it valid.

I decided to not pursue basketball, as the closer I got to college, the more realistic I became about my NBA chances. I didn't know what I wanted to do after basketball, so I took some time away from school and after a few years working various retail jobs, I ended up getting my EMT-B license. To my surprise, I found I loved medicine just as much, if not more, than basketball! The interactions of the various systems fascinated me, and I began to look for ways to progress further in the field.

I began my medical career as a medical assistant at the Heart Hospital of New Mexico in 2005. While working there, I started nursing school, bringing all my negative attitudes about cannabis along with me. These opinions would stay with me for years, now having been cemented by colleagues, superiors, friends, medical journals, and even the media. Because I trusted these sources I did not feel the need to question them—to research for myself if what they were telling me was misinformation or fact.

I received my nursing license four years later, in 2009, and transitioned to working in the CVICU (cardiovascular intensive care unit). I spent most of my nursing career specializing in open-heart recovery for patients who had undergone a bypass or valve replacement surgery. Then, around 2012, my health started to decline. Over time, these issues deteriorated into a serious GI bleed, for which my medical team could not find a source. My usual hemoglobin was 16.5, and at 6'3" even a subtle decline was enough to make me feel nauseated and dizzy. As my hemoglobin continued to drop lower, my appetite disappeared, and my teeth were quickly deteriorating from all the vomiting. I had to take time off work, experiencing a personal low that many of my patients were all too familiar with.

My wife Elizabeth and I had an anniversary coming up, and we decided to celebrate by renting a house in Las Vegas with another married couple we were friends with. While we were spending the weekend together, the other couple brought up the topic of medical cannabis and, knowing of my health problems, told me, "You need to consider this."

This was a shocking suggestion for multiple reasons. They knew of my feelings about cannabis at the time, but even more surprising was that, when I brought it up to my wife, she was accepting of the idea (after weighing the ramifications on my career).

Despite all of my prior opinions and strong beliefs, it didn't change the

fact that I was miserable, couldn't eat, had lost a lot of weight, and could not work. I was at the end of my rope and willing to try almost anything that could help me feel better (a place that many of my patients find themselves in). After considerable soul searching, I told my friends that I would investigate getting a medical card.

Yet even after I got my medical card, I had no idea where to start. Thankfully, the other couple were willing and able to show me the ropes, so I went to their house one night to learn how the process of cannabis preparation and smoking actually worked. My friend's consumption methods were rudimentary at best, but I trusted him enough to humor his lessons on cannabis use.

First, he carefully explained what would happen when we smoked as he began preparing my "rip", as he called it. At the time, he was using a device called a gravity bong, which is a makeshift smoking apparatus made out of an empty bottle (in this case a 20 oz. soda bottle). A space is made on the cap for the bowl, i.e. the cannabis itself, and a hole is made in the bottom of the bottle. The bottle is then filled with water and then, as he said, "You're ready to roll." He lit the bowl and let the water start to flow out, which in turn caused the smoke to be concentrated and pulled into the bottle.

I remember coughing my head off for about three minutes, then changing into swimwear for a dip in the pool before dinner. While I changed, I was still coughing sporadically. I had a burned taste in my mouth, and I remember thinking, "Why would anyone do this?"

I met my friends in their pool and we started talking, the general sort of shooting-the-breeze talk common among all friend groups. About 15 minutes into our swim, I was struck by a startling realization.

I was "high."

This was an incredibly eye-opening moment in my adult life, as there were a few other realizations that quickly came to me:

1) Being "high" on cannabis was not at all what I had been told or expected
2) I had no hallucinations or other psychedelic effects
3) I felt, for the first time in months, no nausea or GI discomfort

And underlying it all, a question: why had I been lied to about this?

CANNABIS AS THERAPY

After my first experience, I knew cannabis couldn't be as harmful as I had been led to believe. It worked better for my nausea than the multiple Zofran I was taking daily ever had. This *had* to be medicine; people, even the so-called experts, were surely just misinformed.

This experience profoundly changed the trajectory of my life. I began to read anything and everything that I could find about cannabis and its medical effects—books, journals, websites, anything. What I began to realize through this research is that many self-proclaimed experts knew about as much as I had before trying it myself. They were relying on what they had been told by others, by "trusted" sources, rather than investigating themselves. In short, they were relying on traditionally accepted psychoactive effects rather than innovation and progress— myths instead of science.

This brought me to another crossroads: if I wanted to share my growing knowledge and have my voice heard and accepted on the matter, I would have to continue my education. Which is why the past three years, apart from researching this book, have been spent pursuing my family nurse practitioner degree.

This is a shocking thing for me to write myself, as I have been very protective of the fact that I had ever used cannabis, due to the taboo and potential ramifications for my nursing license. But it's the truth: *I have benefitted from the use of medical cannabis.*

It is important to note that I also experienced the adverse effects that can go along with improper dosing. After "taking good care of me" the previous few times, my friend got some more potent cannabis, and at the time neither of us understood the importance of proper dosing. He set me up with a little more than I had been using, but as we both failed to realize the increase in potency, this resulted in far too large a dose, causing me to become incredibly dizzy and vomit several times before falling asleep for nearly four hours. Yet despite how horribly I felt initially from using too much (and not knowing at the time how to counteract these symptoms), after waking up I felt amazing. Even more surprising, I was hungry—a sensation which I had not felt in a long time.

This experience changed my life. It helped my illness in a way that nothing had before then, and I am grateful to have experienced even some of the adverse effects of cannabis therapy, as I can now speak more knowledgeably about them with my patients. But more than that, I want to help people in the ways that I have been helped. Now, I look forward to

asking my patients:

“Have you thought about trying cannabis?”

AN INTRODUCTION TO CANNABIS

> "I didn't have a car. [I] took a bus, got five kilos of hashish. [I] went [back] on the bus, and people on the bus, after fifteen [or] twenty minutes, started asking, 'What the hell is that smell!?'"
>
> —RAPHAEL MECHOULAM, *THE SCIENTIST*

"**Can you supply cannabis** to one of my researchers?"

Upon receiving this request, in 1964, Israeli police illegally provided a young Raphael Mechoulam with the first cannabis buds to study at the Weizmann Institute of Science, giving him the opportunity to start unlocking the chemical mysteries of one of the oldest medicinal plants in recorded history. Since the first phytocannabinoid was synthesized in Mechoulam's lab, much has been discovered about how the properties of the cannabis plant impact the endogenous systems of the human body. It has been more than five decades since Mechoulam's first modern studies of cannabis, and the evidence obtained over this period renders its medicinal value unmistakable.

WHAT IS THE ENDOCANNABINOID SYSTEM?

Despite being a relatively recent discovery in terms of body systems, the endocannabinoid system (ECS) is of the utmost importance to understanding the overall homeostatic function of the body (Sinclair, 2016).

This regulatory function is maintained through the three major parts of the ECS (Sinclair, 2016):

1) Various cannabinoid receptors, spread throughout the body

2) Various ligands that interact with the receptors to bring about the homeostatic functions of the body

3) Enzymes that cause the production or breakdown of the ligands

As with any other biological system, there is variability in both structure and function of the ECS between individuals due to both genetic and disease-based causes (Sinclair, 2016).

The discovery and synthesis of THC and CBD by Dr. Raphael Mechoulam and his team in the 1960s was groundbreaking, and one of the first natural progressions from this study was to determine where in the body these phytocannabinoids act (Pertwee, 2006). This additional research led to the discovery and cloning of two receptors in the 1990s, pragmatically named cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) (Prospero Garcia, Rueda Orozco, Belmont, Ruiz Contreras, & Diaz, 2017). Endocannabinoid receptors have been found in mammals, amphibians, birds, and fish (Sinclair, 2016).

THE OANNABIS PLANT

The use of cannabis has long been intertwined with human history and has been cultivated for centuries. Humans have used every part of the plant for a wide variety of purposes, from food to religious ritual. Despite its long history of consumption and industrial use, it remains a controversial topic worldwide. While numerous scientific studies both old and new have revealed few significant health risks and great medical benefit, the consumption of cannabis is still highly stereotyped. Its consumption remains illegal in much of the world, and even in places where it *is* legal, it is highly scrutinized.

WHAT *IS* CANNABIS?

Cannabis is a plant of the Cannabaceae family that has been documented and used for centuries in multiple civilizations, including in religious, ritualistic, shamanistic, and medicinal functions as well as in ropes, textiles, and paper products (Adrian, 2015).

Although the taxonomic classification of this plant has always been difficult due to its genetic variability, the genus Cannabis has been divided into three main species: Sativa, Indica, and Ruderalis (Pellati et al. 2018).

Typically, the cannabis plants has been subject to mono-typing because of the plant ability to easily crossbreed, though the three types have variable uses. Often times, the matter of classification comes down to subjectivity between whether strains of cannabis are *C. Indica* or *C. Sativa* (McPartland & Guy, 2017), while the *C. Ruderalis* is an uncommon, wild-growing strain (Warf, 2014). Since standard methods have proven difficult, the industry has typically been inconsistent in plant classification.

When classifying plants, most are divided by whether the plant has a high concentration of the psychoactive component (A9 tetrahydrocannabinol [THC]) or is rich in other compounds such as cannabidiol (CBD) and other fatty oils (Pellati et al., 2018). The many different cannabis plant varieties have been used in numerous industries historically, and they have recently begun to re-emerge as sources for medicine, industrial fiber, oil, and more.

As cannabis has become much more acceptable in recent years, both legally and socially, there are a few questions that must be addressed. From where did this plant originate? What is its history? How was it used culturally, and why was it both revered and demonized over time?

In this book, we will shed light on those questions as we look not only at the plant itself—how its parts work together and affect the human body for the treatment of disease and general health—but ultimately, at the necessity for providers to understand these aspects that they may better aid in the treatment of their patients.

Chapter 1

ANCIENT HISTORY

> "...Haydar, an ascetic monk who never left his home in the mountains, traveled one day into the nearby fields and came across the cannabis plant. When he returned to his home sometime later, his disciples hardly recognized him because of the 'air of happiness and whimsey in his demeanor,' which was totally inconsistent with his normal personality. He later explained that this change was a result of his having imbibed from the leaves of the cannabis plant..."
>
> —NEWTON, 2013, P. 28

CANNABIS IN HISTORY

A Discovery in Asia

Cannabis originates from Central Asia, where it has been cultivated for thousands (if not tens of thousands) of years. Cannabis was widely used in ancient China, a fact which has been documented through a variety of sources—including carbon dating of ancient cemeteries. Hemp, a cannabis plant that has an incredibly low level of THC, was also used in several textile products including rope, clothing, sails, and bowstrings.

The first documented medicinal use of cannabis was as an anesthetic during surgeries, including those performed on emperor Shen Nung in 2737 BCE (Warf, 2014). Archaeological studies suggest that cannabis was

an important economic commodity at this time, and continued to be a cash crop for indigenous peoples in parts of Xinjiang from the period of the Subeixi culture (1000 BCE to 100 CE) to the Jin and Tang dynasties (around the third to the ninth centuries CE) (Chen et al., 2014).

Eventually, uses of cannabis that relied on its psychoactive properties were suppressed in Japan and China, and would be supplanted in medicine by the use of opium. However, many other regions in southern Asia embraced cannabis and its usage continued as a large part of religious and ritual ceremonies.

Trade Along the Silk Road

The spread of cannabis and hemp at the hands of traders, nomads and even invading armies can be followed through history, beginning in the Asian subcontinent before making its way west throughout Eastern Europe and the Middle East over the next few centuries. In India, cannabis use is well documented in texts such as the Atharvaveda and the Bhagavad-Gita, which showcase it as a celebrated herb with positive therapeutic effects (Warf, 2014).

Cannabis was soon domesticated, becoming a cultivated crop along with the likes of barley, wheat, spelt, and peas. As agriculture began to intensify in the region, evidence of cannabis cultivation could be found as far east as modern Ukraine (Spengler, 2015).

In the following centuries, cannabis spread throughout the Germanic and Norman regions and into Western Europe. Hemp was widely used, just as it had been in Ancient China, as a tremendously versatile textile fiber and was continually cultivated in Europe throughout the Middle Ages. Hemp seeds have been found in the remains of Viking ships, while evidence exists indicating that the Semitic people of the Middle East burned the plant's flower as incense. Several mummies discovered in Egypt contain trace cannabinoids, while pollen was recovered from the tomb of Ramses II, indicating cannabis was available in ancient Egypt. It is even mentioned in writings by Greek and Roman physicians, where its use was so widespread that it was apparently taxed by Roman rulers in the second century CE (Warf, 2014).

Cannabis, Judaism, and the Spread of the Christian Roman Empire

There seems to be no mistaking the prevalence of cannabis use among the Hebrews in the Talmud and then among Christian populations during the first few centuries of the Roman Empire. First mentioned in Exodus, keneh bosem, which translates to "cannabis flower," is a significant ingredient in

anointing oil used in Judaism (Exodus 30:22-23). According to the Pentateuchal description, chrism oil was made by combining cannabis flowers with olive oil and a several other fragrant herbs. The title "Messiah," which holds a great deal of significance amongst the Abrahamic religions, literally means "anointed." This common association between Christians and cannabis would help to explain why the conversion of the Roman Empire to Christianity coincided with a newly levied tax on cannabis throughout the empire.

Meanwhile, cannabis continued to spread throughout Asia, Europe, and Africa, where it found a wide variety of uses. As a medicine, it was recommended for easing a multitude of conditions from headaches to labor pains; it was used in numerous religious contexts; and was often very popular in regions where alcohol was disallowed (Warf, 2014).

Colonization efforts by the European kingdoms aided the spread of cannabis throughout Africa and eventually the Americas, with cannabis cultivation commonly being promoted by monarchs like Queen Elizabeth I and King Louis XIV due to hemp's value in maintaining their naval fleets (Mills 2003). Since most labor of the time was provided by slaves, these individuals became a key component in the economy of the pre-industrial era, establishing an interrelationship between lower class people and cannabis that would eventually become exploited in the early 20th century.

THE PRE-PROHIBITION MODERN WORLD

Asia and the Middle East

Despite the cultivation of cannabis having most likely originated in the Middle East and Central Asia, the authorities of those regions held widely varying opinions on how the plant should be treated. While most of the world agreed that the cannabis plant was the leading source of fabric for making ship sails, clothing, and rope, there were many who were opposed to its consumption (Warf, 2014). Some regions, particularly within the Middle East and Asia, were home to religious sects that held cannabis consumption in very high spiritual regard (Warf, 2014), and some of these sects still follow religious cannabis consumption practices to this day. The Vedas of the Hindu religion praise both cannabis and its psychoactivity (Newton, 2013), while other areas and religions have completely rejected any non-industrial use of cannabis.

Europe, Africa, and South America

After the Napoleonic conquest of Egypt in 1798, hashish, which is a strong, cannabis-derived substance, became incredibly popular in France (Warf, 2014). African colonies, under the rule of the British, Belgians, Portuguese, and others, supplied raw source materials back to their colonizers, leading to a variety of cannabis plant strains and products being quickly transported to Europe and the newly discovered Americas. It was this aspect of the cultural exchange that has led to the modern entanglement of recreational cannabis use in Latin American cultures throughout the 18th and 19th centuries.

North America

Much like the rest of the world, there was a thriving cannabis industry in North America, beginning during its colonization and lasting for hundreds of years thereafter. Having been introduced to America by some of its earliest explorers, cannabis was a highly regarded agricultural product. The first American settlers in Jamestown cultivated cannabis along with their other main crops like wheat, tobacco, and barley (Horn, 2011); King Charles III even issued a decree that the colonies needed to produce *more* cannabis (Griffin, Fritsh, Woodward, & Mohn, 2013). This was due in part to the fact that, while certain varieties of cannabis were commonly used as a treatment for ailments in many parts of the world, hemp remained the primary source of textile fiber for the British Empire.

By the late 1700s, the vast majority of clothing and paper products were being made from cannabis fiber. After the American Revolution, Presidents George Washington and Thomas Jefferson both grew cannabis on their estates (Griffin et al., 2013); Washington's cultivation in particular is well documented in his own ledgers, which prove that he understood the process well, including how to segregate plants by sex ("Founders Online: [Diary entry: 7 August 1765]," n.d.). Cultivated mainly for fiber, cannabis was successful being grown in the Midwest around Illinois, Missouri, and Kentucky during the early 19th century (Cherney & Small, 2016).

Cannabis was a mainstay in the economy of the ancient world, with its primary use being as hemp for industrial purposes. However, its medicinal use has also been well-documented, including its eventual replacement by opium or opium-derived medications, which were stronger than cannabis and held a more potent sedative effect. So, while the practice of using cannabis for the treatment of a variety of ailments might seem novel to modern science, its long history paints a different picture. That being the case, where did the disconnect occur? When did something so profitable

and commonplace become something so maligned and taboo? To answer that question, we must look to the fervor of prohibitionists at the beginning of the 20th century, a movement which would cause a great change in the world's attitude toward cannabis.

Chapter 2

THE PRE-MODERN ERA AND PROHIBITION

> "Sir, it is a little surprising to read in the [British Medical] Journal of May 14 [1938] (p.1058) regarding Cannabis Indica that, 'the active principle has not been isolated.' It *has* been isolated...overforty years ago in the Agricultural Chemistry Laboratory at Cambridge by Wood, Spivey, and Easterfield."
>
> —C.R. MARSHALL, BMJ 6/4/38 P.P. 1233

Cannabis was a widespread and well-known commodity throughout the world by this point, but was beginning to develop a reputation in many regions as an intoxicant consumed by "lower class" people. Yet though the plant has lost favor with ruling classes in many different societies throughout history, there had never been such a tremendous effort to eradicate and regulate a plant like cannabis as would be seen coming into the 20th century.

WILLIAM O'SHAUGHNESSY AND SIR RUSSELL REYNOLDS

The nineteenth century was as an amazing time for modern medicine. The world's first vaccines were developed and used to prevent epidemics;

Louis Pasteur developed germ theory; and physicians began to employ antiseptic measures in their clinics.

Around the same time as modern day aspirin's formulation Irish physician William Brooke O'Shaughnessy, writing in the Bengal Dispensatory and Companion to the Pharmacopoeia in 1842, described cannabis as having no negative medical effect (Warf, 2014). O'Shaughnessy is credited for his extensive work on cannabis and is heralded as one of the first modern physicians to seriously examine its medical value. In his *Text-book of Pharmacology and Therapeutics,* Sir William Hale White extensively outlined the therapies of cannabis, crediting O'Shaughnessy, along with Sir Russel Reynolds, for their research. Reynolds, himself physician to Queen Victoria, recommended medicinal cannabis for restlessness, general paralysis, temper disease in children, irritable stomach, furious delirium, and delirium tremens, among other conditions (White, 1901).

Though not a fan of cannabis use himself, White compares cannabis tinctures to other common medications of the time, such as paraldehyde, but what is key is his note that The text states that cannabis is not a depressant to circulation or respiration; it has no influence on kidneys or other tissues; and it is much less toxic than any sulfides. Comparing cannabis to opium, the textbook states that cannabis has fewer aftereffects, is less toxic, and does not have a significant effect on respiration. Furthermore, it states that cannabis, while less powerful, is preferable to opium, as well as a good substitute for morphine as an analgesic.

CANNABIS IN THE UNITED STATES

Prior to the Food and Drug Act of 1906, all kinds of products were marketed and sold throughout the United States. In the absence of any kind of labeling standard, these products contained any number of ingredients, some of which were poisonous. Due to this lack of standards, physicians of the time were ever wary of snake oil salesmen, individuals promising a miracle cure without giving a hint to the medicine's composition, but the gullible public would often buy their tinctures and potions, hoping for a cure to their ailments.

While cannabis was often an ingredient in these tinctures, there was no standard method in their production or preparation, nor in the strain of the cannabis used, which led to mixed results from various physicians trying to study their potential effects. Some physicians would find their formula

extremely effective in specific conditions, while others would declare it useless (White, 1901). Much like today, "[T]he greatest objection to its employment is variability" (White, 1901, p.p. 327).

RESEARCH iNTO MEDICINAL CANNABiS

It's not surprising that many of the currently accepted medical conditions for which cannabis therapy is common are the same conditions for which cannabis tinctures were used at the turn of the nineteenth century.

Physicians would continually attempt to better isolate the compounds of cannabis, trying to unlock the true medical potential in the plant. However, despite scientists continuing to study the usefulness of cannabis as a tincture, there was a continued acceptance of the demonization of *smoking* cannabis. While companies would commonly sell cannabis "cigarettes" as a treatment for conditions such as asthma, it was not necessarily the physician-preferred method.

Unfortunately, even the slightly more permissive attitude of physicians weren't necessarily shared by the public—or the government. During the early twentieth century, attitudes began to diverge on the best uses for the various strains of cannabis. Public opinion on smoked, recreational cannabis use followed the same logic as alcohol and other vices, becoming a popular target for prohibitionists, while its medicinal use seemed to be tolerated. Even though cannabis was commonly listed as an ingredient in countless medical tinctures and treatments for decades after the Food and Drug Act of 1906, it was the lack of a meaningful distinction between cannabis species that would eventually be manipulated to outlaw the use of cannabis, and for reasons that are all too commonplace: profit.

THE ROOT OF MODERN REGULATION

The historical prohibition of cannabis in the United States is a study in racism, corruption, and greed. While physicians and scientists were busy studying the pharmacological value of cannabis, others were fixated on its recreational use among immigrants, African Americans, and the less affluent, secular members of society.

In 1911, Massachusetts became the first state to ban cannabis as prohibitionist sentiment began to influence state legislators to regulate many "vice" industries, including gambling, prostitution, and alcohol.

While cannabis seemed to fall into this category in regard to recreational usage, physicians continued to prescribe it to a number of patients, having been acknowledged in the U.S. *Pharmacopeia* since 1850 as a known treatment for a very large number of ailments including neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding (White, 1901).

Around the same time, the Mexican Revolution of 1910—1911 caused a great migration of people fleeing the violence of the war into the American Southwest. Although cannabis use was not necessarily popular among Mexicans crossing the border (Campos, 2010), they nevertheless became a popular target for blaming property crimes and unsolved murders. In 1914 in El Paso, Texas, the local government passed the first ordinance banning the sale of cannabis in Texas. Over the following 13 years, ten more states would pass cannabis prohibition laws, including Wyoming (1915), Texas (1919), Iowa (1923), Nevada (1923), Oregon (1923), Washington (1923), Arkansas (1923), and Nebraska (1927).

In many cases, these prohibitions were groundless; states had not been experiencing any problems from cannabis users. The legislators simply hoped to discourage future use, and by the time of the Marihuana Tax Act of 1937, most states had in some way decided to regulate cannabis. But it would be the fears from racism, stoked by the sprawling journalism empire owned by William Randolph Hearst, that would sway the public to allow cannabis to be not just regulated, but outlawed.

RACISM, ANSLINGER, AND REEFER MADNESS

During the 1925 Second Opium Conference and the International Opium Convention, sponsored by the League of Nations and signed in Geneva on February 19, 1925, the United States agreed that cannabis should only be used for scientific or medical purposes. Many pharmacies across the U.S. even carried cannabis-derived tinctures and extracts made by companies like Eli Lily and Parke-Davis. Cannabis “cigarettes” were available for the treatment of conditions such as asthma and bronchitis.

Around the same time, a group of men including Harry Anslinger, William Randolph Hearst, and Andrew Mellon, among others, sought to *criminalize* cannabis. These actors played a role in actively spreading misinformation about the plant and its effects (Holland 2010), even going

so far as to coin the term “marijuana,” a name meant to combine the common Mexican sounding names of Maria and Juana in hopes of igniting existing racial tensions between the United States and newly arrived Mexican immigrants.

However, the individuals responsible for this misinformation campaign were actually attacking *industrial* cannabis, not medicinal or recreational cannabis. Their issue was the lack of differentiation, under U.S. law, between “hemp” strains of cannabis and those with a medicinal value. Industrial cannabis was a competitor to a number of products, including cotton, which was grown in the Deep South. What’s more, industrialists did not like that cannabis could be easily grown by small farmers. And so, they fought to prevent small farmers from having access to such a lucrative cash crop.

A 1938 *Popular Mechanics* article read as follows:

“American farmers are promised a new cash crop with an annual value of several hundred million dollars.It is hemp, a crop that will not compete with other American products. Instead, it will displace imports of raw material and manufactured products produced by underpaid peasant and coolie labor and it will provide thousands of jobs for American workers throughout the land...Hemp is the standard fiber of the world. It has great tensile strength and durability. It is used to produce more than 5,000 textile products, ranging from rope to fine laces, and the wood “hurdes” remaining after the fiber has been removed contains more than seventy-seven percent cellulose, and can be used to produce more than 25,000 products, ranging from dynamite to cellophane.”

The textile uses of cannabis were vast; therefore, it was inevitable that the plant would be targeted by those industries that had the most to gain from its downfall. Prohibitionist fervor was widespread, the fear of immigrants was easy to manipulate; African Americans were also commonly associated with cannabis, and a target of much hatred in the early 20th century Using the public’s fear and disdain for immigrants and African Americans, William Randolph Hearst, owner of the largest newspaper empire in the world, began running sensationalized stories about how cannabis consumption was the cause of countless horrendous crimes. (Hearst personally viewed cannabis, commonly used to make paper, as competition to his sprawling timber forests.)

THE MARIJUANA TAX ACT OF 1937

Together, industrialists—along with Harry Anslinger, nephew of industrialist Andrew Mellon and head the newly created Federal Bureau of Narcotics (FBN)— started a smear campaign about cannabis that spread throughout the United States. Alongside industrial magnates, the FBN was able to stimulate vigorous prohibitionist sentiment concerning cannabis.

Among their efforts, perhaps the most well-known came about when, in 1936, a church group funded a movie called *Tell Your Children* that was meant to scare parents about cannabis. The movie was later purchased and edited by Dwain Esper, who titled it *Reefer Madness*, intending to make a profit and (perhaps unintentionally) fueling the misinformation campaign about cannabis. Despite a lack of evidentiary support from clinical trials or expert testimony, the campaign was effective enough to lead to the Marijuana Tax Act of 1937 which, despite objection from the American Medical Association, was approved by Congress.

Though cannabis-based medicines and the prescription of such were not made illegal by this act, the requirements to prescribe cannabis were made incredibly stringent compared to other medications that most doctors found the process of registering for permits too tedious, or else disliked the newly imposed annual tax or license fee. At the same time, many new medications were becoming available during this time period that seemed more effective than cannabis, and so despite the strongly addictive nature of many of these (usually opium-derived) medications, physicians found them much easier to prescribe. Opioids, unlike cannabis, did not require an additional license or permit to be prescribed by a doctor.

As the medical usage of cannabis declined, it was eventually removed from *U.S. Pharmacopeia* in 1942. But if there still remain any doubts that the restriction of cannabis was motivated by money over morals, consider the Hemp for Victory program. Instituted to combat shortages of domestic goods during the Second World War, the Hemp for Victory program promoted the production of hemp across the nation. However, as soon as the war ended, hemp was re-criminalized and shortly thereafter was further restricted by Congress, who outlined penalties specific to cannabis through the Boggs Act. Under the Eisenhower administration, the Narcotics Control Act of 1956 required that a first offense for cannabis possession carry a minimum sentence of 2—10 years with a fine of up to $20,000. The administration’s strong policy against cannabis would later be further accelerated by its then-Vice President, Richard Nixon.

MODERN LEADERS AND "THE WAR ON DRUGS"

During the 1960s, cannabis use was popularized through the entertainment industry and was widespread among middle class, college-educated young adults. The political climate was becoming highly liberalized in response to decades of militaristic operations in Europe, Central America, and Asia, and the decade would see substantial changes in the areas of civil rights, environmental protections, and anti-war sentiments. However, any hopes of cannabis enjoying a comeback in this more relaxed atmosphere were dashed by the election of Richard Nixon in 1968.

Rejecting the findings of his own commission—the National Commission on Marijuana and Drug Abuse, which concluded that cannabis should be decriminalized—President Nixon declared a War on Drugs in June of 1971 in a national press conference, naming drugs "public enemy number one" (Barber, 2016). Only after Nixon's resignation from office did the movement to decriminalize cannabis pick up steam, leading to more permissive legislation in 11 states. A federal court decision in 1976 allowed Robert Randall, who suffered from glaucoma, to claim cultivation of cannabis as allowable when medically necessary. In 1978, New Mexico was the first state to recognize the medicinal value of cannabis in a case involving a University of New Mexico student Lynn Pierson, who was suffering from cancer. The cannabis legalization movement was supported by the American Bar Association, the American Medical Association, the National Council of Churches, and President Jimmy Carter in the late 1970s (Warf, 2014).

The War on Drugs would be renewed in the 1980s as a new, more conservative Republican administration began to support laws that were "tough on crime." After the election of Ronald Reagan, many conservative states passed mandatory minimum sentencing laws and "zero tolerance" policies, making the approach to all drugs brutally simplistic. These policies led to a large number of arrests and incarcerations for possession of cannabis. Yet despite the massive campaign against cannabis, in 1985 the FDA approved Marinol, a synthetic version of the psychoactive phytocannabinoid THC, as a treatment for nausea. Then, in 1988, the U.S. Drug Enforcement Administration (DEA) asked for a judicial opinion on a 1972 petition regarding cannabis and received a recommendation from Judge Francis Young that cannabis be rescheduled to be medically available for certain conditions. (The next year, however, a DEA

administrator, Jack Lawn, overruled the Young decision, leaving cannabis as a Schedule 1 narcotic that is "highly addictive" and with "no medical value" under federal law.)

The 1990s continued to see tremendous breakthroughs for the relationship between cannabis and the human body. In 1990, the cannabinoid receptor system was discovered and found to be naturally occurring in every human body. Two years later, the first endocannabinoid, anandamide, was discovered, helping scientists understand the phenomenon called "runner's high." Anandamide is our brain's natural version of THC, the psychoactive component of cannabis (Lu & Anderson, 2017). Then, in 1996, California legalized medical cannabis by popular vote, making Proposition 215 the first statewide medical cannabis initiative to officially allow patients to possess, cultivate, and smoke cannabis. By the end of 2000, eight states legalized medical cannabis, including Alaska, Oregon, Washington, Maine, Hawaii, Colorado, and Nevada.

At the federal level, however, a patient's right to choose cannabis as a treatment for his or her condition was not as well protected. In 2001, the US Supreme Court ruled against "medical necessity" as a defense for cannabis cultivation and distribution in a case involving an Oakland Cooperative operation. Then, in 2003, the US House of Representatives rejected an amendment that would prevent federal raids of statesanctioned medical dispensaries by a vote of 273 to 152. In the same year, the US government received a patent on cannabinoids, describing them as neuroprotectants that may help alleviate symptoms of Alzheimer's disease. While more states would join the ranks of California and company in the following years, the federal government would make very few concessions on cannabis until the administration of President Obama.

PRESIDENT OBAMA: A NEW DIRECTION

The Democratic president Barrack Obama was elected in 2008, receiving more votes than any other presidential candidate in American history. Though he was admittedly an avid cannabis consumer through college, President Obama was slow to make any changes in policy toward the plant at the federal level. By 2010, a total of 15 states, as well as Washington D.C., had legalized medical cannabis, mostly by ballot measures during general elections. As a response to state requests for direction from the federal government on medical can nabis measures, attorneys from the

Department of Justice sent letters to state attorneys general threatening to pursue and prosecute medical cannabis producers and dispensers in spite of state-level legalization. Despite the unease caused by these letters, states moved forward with medical cannabis programs.

President Obama's administration did not make any effort to enact changes concerning cannabis until his second term in office, the first measure being the 2013 Cole Memorandum, which instructed federal prosecutors to allow states to regulate cannabis without interference. Then, in 2014, the spending bill completely eliminated any funding that would have been used to investigate and prosecute medical cannabis dispensaries in any of the 23 states that had legalized medical cannabis in some form. When renewed in 2018, the only change was to increase the number of states from 23 to 47. The following year, the Obama administration eliminated one of the obstacles preventing the further study of cannabis and its medical efficacy, the organization known as the Public Health Service Review. This study allowed biomedical researchers much more significant access to cannabis for testing and research.

And so, nearly 80 years after a devastating smear campaign filled with falsehoods and exaggerations derailed research on the therapeutic effects of cannabis, the Obama administration finally allowed further study into the effectiveness of the ancient cannabis plant.

DONALD TRUMP: REVERSING COURSE

The medical cannabis industry has expressed some unease in recent years with the election of Republican president Donald Trump. His appointment of Jeff Sessions, an outspoken opponent of cannabis in every form, as United States Attorney General in 2017 was alarming, especially as the administration began to reverse many of the former president's policies. However, in 2018, with the FDA approval of the pharmaceutical cannabinoid solution Epidiolex, which is commonly known as Cannabidiol or CBD oil, and passage of the US Farm Bill, which legalized industrial cannabis, the medical cannabis industry was put slightly at ease.

Jeff Sessions having since been removed from office as Attorney General, the most recent appointee, William Barr, stated to Congress during his confirmation that although he would support a law that prohibits marijuana everywhere, he would not interfere with state medical cannabis programs that relied on the Cole Memorandum. He then went on to state, "...I think it's incumbent on the Congress to make a decision as to whether

we are going to have a federal system," he said, adding, "This is breeding disrespect for the federal law." (Hutzler, 2019).

Whether the Trump administration will become an obstacle to medicinal cannabis research remains to be seen; however, with nationwide tax revenues of legal retail cannabis sales topping $1 billion in 2018 according to the Institute on Taxation and Economic Policy, cannabis regulation is unlikely to remain unaddressed by the federal government.

Cannabis's history is a long and colorful one. Its importance has ranged from cultural and religious to industrial and economic, from medicinal and therapeutic to being one of the cornerstones of trade and colonialism. Both Eastern and Western societies have alternately regulated and criminalized the possession and usage of cannabis, whether because of misinformation, fear, racism, or for economic and political gain. It has been misunderstood to the extent that the plant's therapeutic and medicinal uses have been "lost" to modern society, and are only now beginning to be rediscovered. Attitudes and policies are slowly changing, but there is so much knowledge to be re-attained, as well as new knowledge to be gained through the aid of modern science and medicine, that we can't afford to waste any time uncovering the potential benefits of cannabis use.

In the next chapter, we will look into the current ethical and legal climate that surrounds cannabis, and the effects this is having on current cannabis research.

Chapter 3

ETHICS IN HEALTHCARE AND CANNABIS-RELATED REGULATIONS

> "The relationship between patient and physician is based on trust and gives rise to physicians' ethical obligations to place patients' welfare above their own self-interest and above obligations to other groups, and to advocate for their patients' welfare. Within the patient-physician relationship, a physician is ethically required to use sound medical judgment, holding the best interests of the patient as paramount."
>
> —AMERICAN MEDIAL ASSOCIATION, OPINION 10.015 (DELANEY & MARTIN, 2016, P. 833)

A healthcare provider has a moral and ethical responsibility to become acquainted with cannabis, its chemistry, and the impact that it has on those that use it, regardless of his or her opinion on its variances in applications. According to the American Medical Association's (AMA) Code of Ethics, "[P]hysicians ... have a professional commitment to prevent disease and promote health and well-being for their patients and the community" (AMA, 2019, para. 2). While medical cannabis has typically been highly scrutinized, it is one of the many possible therapies available to help treat patient illness and provide symptom management. Moreover, the general concern among providers is legal in nature. Despite having federal protections on the matter, providers risk losing their license to prescribe all other medications if they choose to

prescribe cannabis.

In most states where medical cannabis has been made legal, healthcare providers have been able to skirt the legal dangers by issuing recommendations rather than prescribing medical cannabis. This practice draws parallels from past circumstances; in fact, the decline of cannabis prescription at the beginning of the 20th century was caused by the same level of over-regulation. Physicians typically chose opium-derived medications or morphine for prescriptions despite the dangers of their use because it was an easier option. Cannabis was an officially listed medicine in *U.S. Pharmacopeia* editions printed from 1850 until 1942 and was a well-known treatment for a very large number of ailments during that time period internationally. While physicians such as William Woodward, a representative from the AMA, spoke in support of medical cannabis during the 1937 hearing in front of the Committee of Ways and Means, the assault against cannabis by titans of industry like William Randolph Hearst and the DuPont family led to cannabis's current status. The federal government has a longstanding history of stepping between a healthcare provider and his or her patient, and it is unsurprising that physicians are cautious, even now.

ETHICS IN MEDICINE

> "I do hereby affirm my loyalty to the profession I am about to enter. I will be mindful always of my great responsibility to preserve the health and the life of my patients, to retain their confidence and respect both as a physician and a friend who will guard their secrets with scrupulous honor and fidelity, to perform faithfully my professional duties, to employ only those recognized methods of treatment consistent with good judgment and with my skill and ability, keeping in mind always nature's laws and the body's inherent capacity for recovery..."
>
> —THE OSTEOPATHIC OATH
> (AMERICAN OSTEOPATHIC ASSOCIATION [AOA], 2019, PARA. 1)

One of the recurring themes throughout every oath sworn by modern physicians and healthcare providers is that the treatment of a human being as a whole, not just as a condition or illness, is of the utmost importance

(Public Broadcasting Service [PBS], n.d.). Providers have long understood the importance of holding their patient in the highest regard and protecting the relationship of confidence between themselves and those they treat. It is the professional duty of a healthcare provider to allow the patient-physician relationship to remain candid with uninhibited dialogue. While studies have shown that 60—80 percent of patients are dishonest with their doctor about something (Levy et al., 2018), cannabis users are especially less likely to tell their doctor that they use it at all.

It is incredibly important for a healthcare provider to make a patient feel involved in his or her treatment in order to build trust in their relationship. Many patients indicate that one of the main reasons for a failure to disclose an alternative therapy method is that they fear a negative response from their provider and do not want to develop a negative relationship (Kelak, Cheah, & Safii, 2018). Patients are more likely to be forthcoming with their provider when they feel that they are not only being personally respected, but that they know their privacy is prioritized as well (Kelak et al., 2018). There is still a stigma that surrounds cannabis use, despite what seem like obvious therapies, not to mention the proven clinical results. While providers are not always the most outspoken advocates, those who are aware of these therapeutic results typically allow their patients to continue without much negative reaction. However, many providers perceive cannabis to be detrimental to their patients' well-being and disparage its use, causing a rift in their relationship. When patients view a negative interaction with their healthcare provider as an adverse event, it can be incredibly difficult to regain their trust (Levy et al., 2018).

PROTECTING THE PATIENT-PHYSICIAN RELATIONSHIP

When it comes to cannabis as a complementary therapy, providers must be able to have a reasonable conversation with their patients about the therapeutic chemical properties of the medicine. A common problem is that typical language surrounding cannabis is more representational of a recreational intoxicant than of a therapeutic medicine, which has an adverse effect on the provider-patient alliance. Providers who allow their patients the opportunity for shared decision-making and to feel safe in asking questions are able to better maintain the relationship (Levy et al., 2018). Providers who are able to discuss cannabis candidly as therapy are more likely to garner the trust of their patients regarding its use than those

who refer to it in a non-medical manner.

IMPROVING PATIENT OUTCOMES

Recently studies have shown that patient empowerment not only improves health outcomes but also decreases the overall cost of healthcare (Adinolfi, Starace, & Palimbo, 2016). While healthcare providers often have to navigate the line between moral duty and regulation, they most often have done so with the patient's best interest in mind. Moreover, the consistent proof that increasing a patient's ability to choose his or her method of treatment and complementary therapies leads to greater overall health outcomes (Adinolfi et al., 2016). As local and national authorities begin to address cannabis and the derivatives thereof, healthcare providers are more able to discuss the nature of cannabis therapy and the use of such by their patients. Cannabis is being recognized by a number of medical organizations, which add further legitimacy to its value to the medical community such as in the following example:

> "...[T]he compounds present in medicinal Cannabis sativa L., such as A9-tetrahydrocannabinol (A9-THC) and cannabidiol (CBD), and their effects on inflammation and cancer-related pain. The National Cancer Institute (NCI) currently recognizes medicinal C. Sativa as an effective treatment for providing relief in a number of symptoms associated with cancer, including pain, loss of appetite, nausea and vomiting, and anxiety."
>
> —(PELLATI 2018 PARA. 1)

FEDERAL LAW AND PATIENT RIGHTS

> "...[D]octors should not be held liable for conduct that patients might engage in after leaving the office and that open and unrestricted communication is vital in preserving the patient-doctor relationship and ensuring proper treatment."
>
> —(CONANT V WALTERS US COURT OF APPEALS, NINTH CIRCUIT)

As of 2002, a federal court decided healthcare providers cannot have their license revoked solely for the recommendation of medical cannabis. This instrumental court case, Conant v. Walters, protected the relationship between a provider and his or her patient, stating that a doctor can be candid without fear of punitive measures when prior to this ruling the federal government had threatened revocation of licenses for prescribing cannabis. One of the remaining concerns among providers is that if they prescribe cannabis, they may be disallowed to prescribe all other medications. This is strikingly similar to the time period in the 1930s and 1940s when physicians were required to obtain a special license and pay additional fees in order to prescribe cannabis. Providers today avoid negative recourse by the federal government with a recommendation of cannabis therapy rather than a written prescription of cannabis itself.

More recently, a 2013 memorandum written by then-Attorney General Cole to the Department of Justice provided instruction on how local departments should proceed with federal enforcement and regulation of cannabis. The memorandum states that people and businesses acting in accordance with state rules will not be subject to federal encroachment. Essentially it gave each state that had initiated a medical cannabis program the opportunity to control and monitor the industry. William Barr, the current Attorney General at time of publication, has offered assurances of protection from federal encroachment to businesses following the *Cole Memorandum*, however, the issue at the Federal level still remains relatively transient.

Most of the focus on cannabis law, especially for medical cannabis patients and their providers, falls at the state level where many different regulations can affect the industry. The Federal Spending Bill passed in 2014 included a rider that eliminated any funding that would be used to police state-sanctioned cannabis activity, which was renewed in 2018. As an indicator that the issue of cannabis in a medical capacity may soon be addressed by the federal government, the 2018 Farm Bill legalized industrial cannabis at a federal level. States are developing individualized strategies on how to best regulate this new industry.

STATE LAWS

The laws on cannabis, its products, and its use can vary widely from state to state. Some states have legalized cannabis as a recreational product; others only allow certain forms of cannabinoid derivatives. Also, as more

states enact more regulations, the law will develop from year to year. There are numerous consistencies between many states. However, there is no standard. The following are states with established legal medical cannabis programs and/or dispensaries:

Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
Florida
Hawaii
Illinois
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Missouri
Montana
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Dakota
Ohio
Oklahoma
Oregon
Pennsylvania
Rhode Island
Utah
Vermont
Washington
West Virginia

Almost every state in the U.S. has begun to explore the legal framework

that is necessary to provide patient access to cannabis-derived products. While some states have long-standing medical cannabis programs, others have newly created and stringent restrictions. A few states have taken no action to allow patient access to cannabis products, and others have created laws that allow certain medical conditions to qualify patients for affirmative defense against prosecution while creating no pathway to manufacture or obtain cannabis products. Navigating each state's individual mandates on cannabis access can be difficult; however, understanding how medical cannabis laws affect patients is necessary to cultivate a successful patient-provider relationship.

Most states that allow access to medical cannabis list specific medical conditions or circumstances in which a healthcare provider may recommend cannabis. While some states are more restrictive regarding allowable conditions, the following can be regarded as generally acceptable disease states or medical conditions for which cannabis can be recommended:

- Cancer
- Glaucoma
- Human immunodeficiency virus (HIV)
- Acquired immune deficiency syndrome (AIDS)
- Chronic or debilitating diseases or treatment for such diseases, which produces cachexia, severe pain, severe nausea, seizures, or persistent muscle spasms

Some states have allowed for additional conditions to receive approval pending further discovery into the efficacy of cannabis as a treatment. Success has since been seen in several other conditions, like amyotrophic lateral sclerosis, Crohn's disease, agitation in Alzheimer's disease, as well as the treatment of these conditions.

State Medical Cannabidiol Oil Programs

While many states have, by a legislative or elected proposition, allowed cannabis to be distributed and used in many forms, other states have chosen more restrictive programs. For example, several states allow patients with certain conditions to obtain Cannabidiol (CBD) in oil for ingestion. In many states, specific conditions have been defined through legislation as allowable for CBD recommendation. For example,

Alabama's law allows "cachexia or wasting syndrome; severe or chronic pain; severe nausea; seizures; severe and persistent muscle spasms" (Carly's Law, 2014). The FDA has approved two pharmaceutical cannabis-based drugs, Epidolex and Sativex; however, they are not readily available or easily prescriptible because the formula of each medication is individualized according to the exact patient as of 2019.

In addition to a high level of difficulty in obtaining CBD products in many states, there are a host of hemp-derived products on the market that have virtually no therapeutic value despite being marketed as such. Also, states have individual limits on the level of allowable THC in a CBD product, some as high as 5% and others being as low as none (0.0%) allowed. This level of complexity has created an understandable level of uncertainty among the patient population. As a provider, it is necessary to be familiar with the CBD products with actual medical value available in each individual state. States that only allow the use of Cannabidiol in certain circumstances are as follows (allowable THC in total percent):

Alabama (3%)
Georgia (5%)
Idaho (3%)
Indiana (0.3%)
Iowa (3%)
Kansas (0.0%)
Kentucky (0.0%)
Mississippi (0.5%)
North Carolina (0.9%)
South Carolina (0.9%)
Tennessee (0.9%)
Texas (0.5%)
Virginia(5%)
Wisconsin (0.0%)
Wyoming (0.3%)

Affirmative Defense

Rather than having actual medical cannabis programs where dispensaries have been created, some states have either legislatively or judicially allowed certain medical conditions to be an affirmative defense to cannabis possession. Patients may seek out and obtain CBD products to treat a specified condition and, if caught, they can use an affirmative defense of medical necessity as the defense when facing prosecution.

Kentucky legislators, on the other hand, simply removed CBD from the definition of marijuana under its controlled substances act but have otherwise not addressed allowing patient access.

While a healthcare provider's duty to understand cannabis and its usage for treating patients is clear, where a provider stands with the law on this issue is not so clear. It is because of these muddy legal waters that providers must also acquaint themselves with the laws in their own state. The reality is that a patient who is interested in cannabis may likely seek this treatment as an individual, instead of under the protection of the provider-patient umbrella and thus undermining this vital relationship.

To better aid the provider in their understanding of cannabis, the next chapter will cover the body's own receptors that allow the plant to have its therapeutic effects—the part of the body known as the endocannabinoid system.

Chapter 4

THE ENDOCANNABINOID SYSTEM

> "The endocannabinoid receptors, the endocannabinoids, and their biosynthetic and biodegrading enzymes constitute what has come to be known as the endocannabinoid system, the discovery of which prompted a search for its physiological and pathophysiological roles. This search revealed that there are several disorders in which endocannabinoids are released to their receptors in an "autoprotective" manner that ameliorates unwanted effects of these disorders."
>
> —(MECHOULAM, HANUS, PERTWEE, & HOWLETT, 2014, P. 761.)

The discovery of the endocannabinoid system (ECS) in vertebrates was not only an amazing scientific accomplishment, but one which has played an instrumental role in aiding our understanding and analysis of the relationship between cannabinoids and homeostasis. Scientists are just now beginning to unravel the connection between phytocannabinoids and terpenes found in certain plant species and how they interact with receptors present in the human body. Furthermore, though the relationship between the various chemical compounds produced in cannabis species and their combined effect on the endocannabinoid system is complicated, there is a wealth of evidence that supports the positive relationship between human health and the endocannabinoid system.

DISCOVERY AND HISTORY

The discovery and synthesis of THC and CBD by Dr. Raphael Mechoulam and his team in the 1960s was groundbreaking, and one of the natural progressions from this research was to determine where precisely in the body these phytocannabinoids acted (Pertwee, 2006). This led to the discovery and cloning of two receptors in the 1990s, unironically named cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) (Prospero Garcia, Rueda Orozco, Belmont, Ruiz Contreras, & Diaz, 2017).

These endocannabinoid receptors, or analogues of them, have been found in mammals, amphibians, birds, and fish (Sinclair, 2016). In fact, *all* vertebrates have been found to have an endocannabinoid system (McCamman, 2017), one which plays a crucial role in the overall homeostatic function of the body (Sinclair, 2016).

The ECS is considered to be a "homeostatic gatekeeper" of the immune system (Olah, Szekanecz, & Biro, 2017), a maintainer of regulatory function regulated through the three major parts of the ECS (Sinclair, 2016):

1) Various cannabinoid receptors spread throughout the body
2) Various ligands that interact with the receptors to bring about the homeostatic functions of the body
3) Enzymes that cause the production or breakdown of the ligands

The regulatory functions that the endocannabinoid system plays a role in include: gastrointestinal (GI) function, appetite, metabolism, pain, memory, movement, immunity, inflammation, neuroplasticity, learning, and emotional modulation (Mouhammed et al., 2018) The receptors of the ECS are part of the G-protein-coupled receptors (GPCR) a superfamily of genes that play an enormous role in the cellular function of humans (Bow & Rimoldi, 2016) (Lu & Anderson, 2017). There are roughly five classes of GPCR, with CB receptors falling into the rhodopsin-like family of G-protein coupled receptors (Bow & Rimoldi, 2016). (Note that there is currently debate between five or six classes of GPCR, due to ongoing research.)

ENDOCANNABINOID RECEPTORS

The endocannabinoid system is a major part of the body's regulatory function and has receptors that are scattered throughout the body. To give perspective of how important the ECS is, there are ten *times* more cannabinoid (CB) receptors in the body than opioid receptors, and is unique in that it has both intra- and extra-cellular receptors (Maida, 2018). As a result of this discovery, a past major concern can be alleviated—that of overdosing on cannabinoids. As the brainstem has very few CB receptors, overdose is a physiologic impossibility (Maida, 2018). In fact, a statement published in 1988 in the NIDA factfinder says:

> "At present, it is estimated that marijuana's LD-50 is around 1:20,000 or 1:40,000. In layman terms this means that in order to induce death, a marijuana smoker would have to consume 20,000 to 40,000 times as much marijuana as is contained in one marijuana cigarette. NIDA-supplied marijuana cigarettes weigh approximately .9 grams. A smoker would theoretically have to consume nearly 1,500 pounds of marijuana within about fifteen minutes to induce a lethal response."
>
> —(YOUNG, 1988)

CB1 Receptors

The CB1 receptors are primarily located in the central nervous system (CNS), with expression being focused in the motor and limbic regions as well as areas involved in pain transmission and modulation like the periaqueductal grey (PAG), Rostral Ventromedial Medulla (RVM), and spinal cord dorsal horn (Ulugol, 2014). In the periphery, the CB1 receptor expression is found in the peripheral nervous system (PNS), the gastrointestinal tract (GI), smooth muscles, spleen, tonsils, uterus, prostate, and adrenal glands (Bow & Rimoldi, 2016). Despite the high concentration of CB1 receptors in the brain, there is a very scant distribution in the brainstem, which controls both the heart and lungs. As previously stated, this sparsity of receptors might give insight into the overall absence of cannabis overdose-related deaths (Sinclair, 2016).

CB2 Receptors

While CB1 receptors have a central focus, CB2 receptors are concentrated in the peripheral nervous system and centralized around immune cells, with lesser expression in the GI tract, sensory neurons, and CNS (Prospero Garcia et al., 2017) (Sinclair, 2016). The expression of CB2 receptors in

immunologic locations such as in hematopoietic cells and in immune cells (spleen, tonsils, bone marrow and leukocytes) (Lu & Anderson, 2017). CB2 is the less studied of the cannabinoid receptors (Ulugol, 2014; Bow & Rimoldi, 2016). Because of the lack of study and the dense immunological expression, CB2 receptors were originally consigned to the role of immunologic mediator, but this receptor does so much more (Bow & Rimoldi, 2016). Due to the influx of new research, we are now finding that the CB2 receptors role is much larger, being that of a general protective system (Dabrowski & Skarjda, 2017). This is because of how these receptors have been found to be added or deleted in areas of disease and times of extreme stress (Dabrowski & Skarjda, 2016). To this point, there is enhanced expression of CB2 receptors in Alzheimer's disease, with this expression being focused around the amyloid plaques that are a hallmark of the disease in an attempt to mitigate the spread of the disease and reduce inflammation (Bow & Rimoldi, 2016; Dabrowski & Skarjda, 2017). These receptors also have an increase in the rate of expression when inflammation is present in the body, which has the potential to partly explain the ECS's role in the body's endogenous response to injury (Sinclair, 2016). This led Dabrowski & Skarjda (2017) to note that the ECS has a role in general protection, immunity, and homeostasis (Dabrowski & Skarjda, 2017).

G-Protein-Coupled Receptors (GPCR)

Both cannabinoid receptor types are G-protein-coupled receptors (GPCR), with the main role of both being modulators to the release of chemical messengers (Pertwee, 2006). CB1 and CB2 receptors share about 48% of their amino-acid sequence identity (Dabrowski & Skarjda, 2017). These receptors bind to both endocannabinoids and phytocannabinoids equally with specificity akin to a lock and key (Sinclair, 2016; Lu & Anderson, 2017). The activity of endocannabinoids tends to take place mostly pre-synaptically rather than post-synaptically (Sinclair, 2016). This shows that "these molecules work as retrograde synaptic messengers, traveling back over the synaptic CB1/CB2 receptors to inhibit the release of neurotransmitters stored there" (Sinclair, 2016, p. 1G9). The location of CB receptors in the brain help facilitate the receptors' blocking of neurotransmitters (Dabrowski & Skarjda, 2017). CB1 receptors are primarily located presynaptically on the axons and terminals. This allows the receptors to control the flow of neurotransmitters. This activity is accomplished through the use of single or combined inhibitory methods including the inhibition of adenylate cyclase, by impeding the voltage

change needed to open calcium channels, or/and through the activation of potassium channels (Ulugol, 2014). CB2, while primarily located outside the CNS, still produces inhibitory effects through the release of adenylate cyclase rather than blocking of the calcium or potassium channels (Ulugol, 2014).

As research programs further explore the ECS, knowing that the CB1 and CB2 receptors are G-coupled-protein receptors, several other similar receptors are being considered as possibly cannabis reactant due to their interaction with both endocannabinoids as well as phytocannabinoids, including GPR 55 and GPR 119 (Lu & Anderson, 2017; Sinclair, 2016). For the same reasons, transient receptor potential vanilloid type I (TRPV I) are also being explored as endocannabinoid receptors (Lu & Anderson, 2017).

ENDOCANNABINOIDS

As stated, the ECS is a lipid signaling system involved in many physiologic and pathologic functions, with the overall goal of maintaining homeostasis (Lu & Anderson, 2017). To execute this maintenance, the primary signaling agents for the endocannabinoid system are endocannabinoids, or endogenous cannabinoids. Endocannabinoids are biologically active lipids that activate endocannabinoid receptors (Lu & Anderson, 2017; Sinclair, 2016).

Endocannabinoids have been referred to as "the body's own marijuana" because they affect the very same receptors that phytocannabinoids act on (McCamman, 2017). An interesting difference to note between traditional neurotransmitters and endocannabinoids is their synthesis and storage. Neurotransmitters such as serotonin or dopamine are synthesized as the body is able to make them and stored in the vesicles of the brain, whereas endocannabinoids are synthesized on demand, in response to the homeostatic needs of the body (Sinclair, 2016; Huang, Chen, & Zhang, 2016).

Anandamide

The first of the endocannabinoids to be discovered, anandamide, was first found in a pig brain, where it was identified by Mechoulum and his team in 1992 (Bow & Rimoldi, 2016; Lu & Anderson, 2017; Sinclair, 2016). The name "anandamide" comes from the Sanskrit word "*ananda*," which is translated to mean "supreme joy" or "bliss" (Lu & Anderson, 2017;

Sinclair, 2016). The distribution of anandamide throughout the body mimics the distribution of CB1 receptors. This is because anandamide has a higher affinity for CB1 receptors, although still exerting some CB2 effect (Sinclair, 2016; Lu & Anderson, 2017). Outside of the effects that anandamide has on endocannabinoid receptors, it has been found to have an effect on other receptors such as the transient receptor potential vanilloid type I (TRPVI) receptors (Skaper & Marzo, 2012).

2-Arachidonoylglycerol (2-AG)

2-arachidonoylglycerol (2-AG) is the other majorly studied endocannabinoid. The known modulatory effects of 2-AG include feeding, hypotension, neuroprotection, cell proliferation, and many others (Bow & Rimoldi, 2016). This is amazing considering the fact that this endocannabinoid has such an important homeostatic role in the body, and it originally was considered to be insignificant (Bow & Rimoldi, 2016). The homeostatic role is shown to be the maintenance of immunity, as 2-AG has been found to be in both bovine and human breast milk (McCamman, 2017). Basal levels of 2-AG have been noted to be one thousand times higher in the brain than levels of anandamide (Zou & Kumar, 2018).

Additional Endocannabinoids

The ECS has yet to be fully explored, and few studies exist documenting the full list of known or possible endocannabinoids. There is documentation of recently discovered endocannabinoids Oleamide (9-10-octadecenomide, ODA) Virohamine (VIR), N-arachidonoyl dopamine (NADA), and Noladin-ether (N-E) (Prospéro Garcia, Rueda Orozco, Belmont, Ruiz Contreras, & Diaz, 2017). These are more recently discovered, and their effects have not been well documented (Prospero Garcia et al., 2017). There is great potential as further scientific studies unlock the relationship between endocannabinoids and homeostasis.

The endocannabinoid system is an extremely important system that regulates functions within the human body and is comprised of receptors that are affected by endocannabinoids, which are produced by the body, as well as phytocannabinoids that come from the cannabis plant. The overall homeostatic effects of this system are of the utmost importance to the day-to-day physiologic functions of the body. With this understanding of, and appreciation for, the critical role the ECS plays in the body's self-regulation in hand, the next chapter will cover the plant itself, its varieties,

and its many uses.

Chapter 5

THE CANNABIS PLANT

> *"Cannabis Sativa,* best known as the source of marijuana, is probably the world's most recognizable, notorious and controversial plant. Because of its criminal association, almost all research and economic development—both narcotic and non-narcotic aspects— were suppressed for most of the 20th century."
>
> —(SMALL, 2015, P. 190.)

Much of the debate surrounding cannabis and its variety of uses has been informed (and stymied) by its categorization as an intoxicant, one listed by the Drug Enforcement Agency (DEA) as a schedule I narcotic. Yet extensive study and investigation have largely disproven the commonly held beliefs and negative stigma surrounding cannabis, while recent examination into the biological and chemical processes have provided a wealth of insight into the therapeutic and textile possibilities of cannabis-derived products. It is therefore to the benefit of the discussion to take an unbiased look at the cannabis plant and examine what it *is* and *isn't,* rather than what it might or might not be.

GENUS AND SPECIES

Cannabis is one of two primary plant species that make up the

Cannabaceae family (the other being *Humulus,* best known for its member *H. Lupulus,* or hops, the main ingredient in beer).. Evidence of its domestication and cultivation date back thousands of years, yet while there have been a variety of terms used to distinguish the differences between plants, the exact distinction between species has become increasingly subjective.

In fact, the plant's incredible versatility for crossbreeding and hybridization has led many to the assumption that the different species cannot be appropriately classified, leading to the use of the singular term *Cannabis Sativa* as appropriate when describing the entire species (Small, 2015).

Typically, however, for clinical and industrial application, the nomenclature has been expanded to three main terms: *Cannabis Indica, C. Sativa,* and *Hemp* (Mcpartland & Guy, 2017). (Although these terms are used to describe the variation in species of cannabis, they have not always been used consistently when describing individual plant species and their offspring.) At this point, the best way to classify cannabis plants is by using the terminology that best meets the standards of *The International Code of Nomenclature for Algae, Fungi, and Plants,* which are *Cannabis Sativa* and *Cannabis Indica* (Mcpartland & Guy, 2017). Although it is very common that strain names and popular nomenclature misrepresent the true nature of individual plant species ancestry, when comparing alleles between *C. Indica* and *C. Sativa* it is apparent that they are two distinct species. And upon additional comparison between alleles present, *C. Indica* plants are more closely related to hemp than *C. Sativa* (Sawler et al., 2015).

Cannabis Indica

Cannabis Indica plants are short and stocky with wide leaves and have a long vegetative growth period. They have a short flowering period and do not increase significantly in height once they reach the flowering phase. *C. Indica* seems to have originated in the central Asian region of modern-day Pakistan and Nepal ("Sensi", 2019). *C. Indica,* when labeled by perceived clinical effect, is described as being both a sedative and muscle relaxant. Additional effects can vary depending on each individual plant's genetic structure and lineage.

Cannabis Sativa

Cannabis Sativa plants grow tall, have narrow leaves, and originated in more equatorial regions of the Asian continent around modern-day

Thailand. They also have a distinct set of genetic markers (Sawler et al., 2015). *C. Sativa* plants have a long flowering period in which they may grow double or triple their vegetative size ("Sensi", 2019). The perceived clinical effects of a *C. Sativa* plant are typically psychological and stimulatory in nature. Additionally, like *C. Indica*, various strains labeled *C. Sativa* can have a variety of effects depending on each individual plant's genetic structure and lineage.

Hemp

Hemp generally grows taller than *C. Indica* or *C. Sativa,* its leaves are grouped closely together at the top of the stem, and it is hardy in most climates. Hemp is actually the oldest textile fiber and possibly the original industrially-used product of humankind. While the *Encyclopedia Britannica* ("Hemp," 2018) describes hemp for textiles as being recorded in ancient Chinese documents around 2800 B.C., additional sources suggest much earlier industrialization of hemp (Small, 2015; Sawler et al., 2015). Hemp is known for its sturdy structure and fibrous consistency. Hemp is more closely related to the *C. Indica* than *C. Sativa* plant. Genetic typing has proven that hemp ancestor *C. Indica* interbred with other species of plants that produced hemp as we know it today (Sawler et al., 2015). A re-emergence in the interest in industrial hemp has led to its further investigation and definition legally and scientifically.

Hemp plants are known to have relatively low amounts of THC and are legally defined by the U.S. government as having less than 0.3% THC. They are typically rich in CBD, however, and have a variety of other positive qualities. Currently, the applications for hemp are widespread from cloth to food products ("Hemp", 2018). CBD oil derived from hemp plants has become readily available in most U.S. states, while additional hemp-based products have been approved by the FDA.

Hybridization

C. Indica and *C. Sativa* can easily interbreed with each other, producing offspring that have a combination of traits from both species. Various plants have been selectively bred for specific traits such as high flower yield or increased levels of THC. As the medical cannabis industry has expanded, selective breeding has led to an array of hybrid species with colorful names and descriptions. Their traits are variable and need to be better defined by their specific cannabinoid-terpene compound mixture.

Sex

Cannabis is normally a dioecious species, meaning the male and female are present as separate plants; however, through the process of domestication, humans have turned it into a mostly monoecious species while also heavily favoring female plants (Small, 2015). In fact, through breeding and cloning techniques, some species of cannabis have been developed to be female-only and are especially prevalent in the production of therapeutic cannabis. This is because pollinated female cannabis plants will produce seeds and are less potent in THC than those that do not interact with male plants. Therefore, male plants are selectively culled from cannabis crops that are being used for therapeutic purposes. On the other hand, in hemp that is being used for industrial purposes, it is favorable for plants to become pollinated and produce seeds.

Male cannabis plants, so called for their stamen, are typically taller yet less robust than females, with fewer leaves. These males only serve the purpose of producing pollen, with fertilization occurring by wind transference. The male's pollen can be blown over long distances and can pollinate many female plants. The plants die after shedding their pollen, unlike the females that can live for years (Small, 2015).

Female cannabis plants are named such for their carpels and have larger leaves and stronger stalks than the male plants. Throughout its history of domestication and cultivation, female plants, similarly to livestock, have been found to be more productive than their counterparts (Small, 2015), as the female plants produce flowers and are a greater source of fiber than males.

In most circumstances, growers of cannabis plants have systematically controlled pollination. Of note, cannabis plants *can* be self-pollinating, and were likely evolutionarily such until human intervention (Small, 2015). Now, plants with both carpels and stamens, commonly called hermaphrodites, negatively impact crops through unwanted pollination. Yet in situations of environmental stress or other circumstances, a female plant can grow stamens on some of its branches. These hermaphroditic plants are typically culled much like male plants, despite having the potential to flower like females.

PRACTICAL USES FOR CANNABIS

The uses for cannabis and hemp plants are potent and extremely varied, with the main purposes for its use being categorized as medical, agricultural, or industrial.

Medical

The medical cannabis industry has reached more than $1 billion and is growing rapidly each year (Ward, Thompson, Iannacchione, & Evans, 2019). More states have expanded patient access to medical cannabis, and some have even created a recreational market that allows all adults cannabis access. As of 2019, many synthetic cannabis-based medications are in the late stages of clinical trials or have received FDA approval. The leading company currently producing and testing synthetic cannabis derivatives is GW Pharmaceuticals, but there are other companies working on similar medications (Mintz, Nison, & Fabrizio, 2015). While some of these drugs show promise, the entourage effect cannot be denied, and studies have confirmed that individual cannabinoids aren't as effective as the entire group in most therapeutic capacities.

The use of medical cannabis has been documented historically for thousands of years, and only in the last century did it become the subject of intense scrutiny. Early modern scientists and botanists, like William O'Shaughnessy, first wrote about cannabis and its effects while being readily prescribed in Europe and North America until just after World War II. Cannabis was referenced in the first eleven editions of the *U.S. Pharmacopeia* and was the primary ingredient in numerous tinctures and medicinal elixirs. After a few decades, Dr. Raphael Mechoulam further studied the chemical structure of cannabis, which inspired the discovery of countless interactions between the human body and cannabinoid-terpene compounds found in cannabis. Within the last 10 years, cannabis has become demonstrably effective as a treatment for many conditions.

Agricultural

Hemp was used for thousands of years to make a tremendous number of textiles and was a primary crop of ancient China, through which its cultivation rapidly spread across the globe, with *Cannabis Sativa* and *Indica* being traded across cultural, lines as well.

Hemp and cannabis plants are also both edible, and the seeds they produce can be used for oil extraction or processed into a usable flour. The seeds are a good source of protein and are used in a variety of products from energy bars to beer, although such products are usually imported into the United States from places like Canada. Recently, several restrictions have been lifted at the federal level allowing some farmers to take advantage of this robust crop. As hemp becomes more readily available and less expensive, it is likely that American businesses will have a better opportunity to explore its viability as a staple for farmers.

Industrial

One of the main obstacles for using hemp industrially has been a legal one, but now that American businesses are finally being allowed to explore the possibilities, many new products are entering the market which are made entirely from hemp. One of the most promising items in this outpouring of products is a plastic-like line of products including toys, cookware, and car parts, all of which are biodegradable (Cannopy Corporation, n.d.). Additionally, there are products for a wide range of industries such as construction materials and apparel. Much like at the turn of the 20th century, more industries are beginning to explore the possibilities of hemp products.

Cannabis is a deceptively simple plant with a host of positive applications and uses beneficial and well-suited to modern society. With legal restrictions relaxing and more and more research being conducted, we have only begun to scratch the surface of what this plant can offer. However, the primary topic of discussion remains the effects of the plant on the human system, and so the next chapter will cover the chemical makeup of the plant and how each aspect impacts the human body.

Chapter 6

THE CHEMISTRY OF CANNABIS

> "[Cannabis] is characterized by a complex chemical composition, including terpenes, carbohydrates, fatty acids and their esters, amides, amines, phytosterols, phenolic compounds, and the specific compounds of this plant, namely, the cannabinoids."
>
> —(PELLATI, 2018)

The cannabis plant can be easily analyzed at the chemical level, and as its structure becomes revealed, it's easy to see why this particular plant has so many therapeutic properties. There are numerous compounds found to be synthesized within the plant itself through regular growth and development, while other compounds develop in greater amounts through aging and curing of the plant's flowers. As we gain more understanding into the chemistry of the cannabis plant, so, too, do we better understand the combined/entourage effects of the chemicals within the plant itself. This section will explore the chemistry of cannabis, its structure, and the phytocannabinoids that impact the endocannabinoid system within the human body.

"CANNABINOIDS"

On the chemical level, cannabis is broken down into endocannabinoids, of

which there are two types: phytocannabinoids and endocannabinoids (Bow & Rimoldi, 2016). Endocannabinoids and phytocannabinoids are currently grouped together under the umbrella term "cannabinoids," but this is poor nomenclature, doing neither group justice in classification while also implying interchangeability of the terms (Greydanus & Merrick, 2016). Endocannabinoid is short for "endogenous cannabinoid" or a cannabinoid that is made endogenously, by the body (Lu & Anderson, 2017). Phytocannabinoids are cannabinoids that are synthesized by the cannabis plant itself (Russo, 2011).

Endocannabinoids are of the utmost importance to the body's maintenance of homeostasis and have a unique relationship with the phytocannabinoids found in the cannabis plant. Currently, there have been more than 700 phytochemicals or biologically active compounds identified in plants, many of which are in cannabis plants (Sinclair, 2016). Yet despite hundreds of phytochemicals having been found in the cannabis plant, researchers are currently only beginning scraping the surface of what there is to know about phytocannabinoids. While Δ^9-tetrahydrocannabinol, Δ^9-THC, or THC, is the most well-known and studied of the phytocannabinoids, there are several others that have large effects on the body (Greydanus & Merrick, 2016).

DISCOVERY

While many believe Mechoulam, the father of modern cannabis science, to be the first to have isolated phytocannabinoids in 1963, cannabinol(mistaken to be the psychoactive component in cannabis) was actually first isolated in the late 19 th century (Atakan, 2012) by Wood, Spivey, and Easterfield (White, 1901). However, Mechoulam *was* one of the first scientists to isolate Δ^9-THC in 1964, which is the most well-known phytocannabinoid (Freeman et al., 2016; Hand, 2016).

Following this discovery, scientists were able to begin unfolding the mysteries surrounding the clinical value of phytocannabinoids and how they interact with the human body. It would be almost 25 years after the isolation of Δ^9-THC that the endocannabinoid system would be discovered (Hand, 2016; Freeman et al., 2016). More recently, a significant number of studies have affirmed the pharmacological value of the phytocannabinoids found in the cannabis plant.

PHYTOOANNABINOIDS

Phytocannabinoids, like endocannabinoids, are lipophilic in nature, being fatty compounds that have a proclivity for adipose tissue (Bow & Rimoldi, 2016) (Klumpers & Thacker, 2019). These compounds have been isolated and subdivided into 11 different chemical classes that are synthesized and stored in the cannabis plant as cannabinoid acids (Pellati et al., 2018) (Atakan, 2012). The development of all cannabinoids stems from cannabigerolic acid (CBGA), the base from which the acidic forms of all other cannabinoids are derived (Pellati et al., 2018). The acidic forms of phytocannabinoids contain a carboxyl group and are the precursors to the active forms of cannabinoids (Pellati et al., 2018. Conversion of phytocannabinoids to the active form through the removal of the carboxyl group, known as decarboxylation, occurs either actively through heating or passively through light (Nahtigal et al., 2016; Pellati et al., 2018). Through this decarboxylation, the acid forms of phytocannabinoids are converted to their active forms; for example, A9-tetrahydrocannabinol acid (THCA) becomes the active form of A9-t etrahydrocannabinol, or the better-known THC (Pellati et al., 2018; Atakan, 2012). The biosynthesis of the cannabinoid acids occurs at a ratio that is genetically determined by each individual plant (Atakan, 2012). This is similar to the individual differences in human endocannabinoid expression. The current list of actively researched phytocannabinoids includes A9-THC, CBD, CBG, CBC, CBN, THCV, and CBDV with more being discovered regularly (Schley, 2017). The effects of the individual phytocannabinoids will be further explored in this chapter.

There are multiple groupings of phytocannabinoids, but for current purposes we will focus on three (Pellati et al., 2018).:

1) Naturally occurring or acid forms

2) Decarboxylation through heat

3) Decarboxylation through aging

CBGA (cannabigerolic acid) is the precursor to all other cannabinoids, with the development of cannabichromenic acid (CBNA), Δ^9-tetrahydrocannabinol acid (THCA), and cannabidiolic acid (CBDA) being known and well-studied (Pellati et al., 2018). These phytocannabinoids present on the plant in their acidic form on the trichomes of the plant (Nahtigal et al., 2016). Trichomes are external protuberances that cover the

plant in a “sticky” residue that has been found capable of trapping insects (Nahtigal et al., 2016). Not as much research has been done into the medical effects of the acidic forms of phytocannabinoids. There is some research that shows there is a pharmacologic benefit to these effects, but more research is needed. The current consensus seems to be that the acidic forms of the phytocannabinoids have similar, but reduced effects of the decarboxylated form, without the psychoactivity (Russo, 2011; Pellati et al., 2018). For the purposes of this book, we will focus on the effects of the cannabinoids that the patient will be using as their medication—specifically, the activated or decarboxylated form.

NATURALLY OCCURRING PHYTOCANNABINOIDS

Δ9-tetrahydrocannabinol (THO)

While Δ^9-tetrahydrocannabinol (THC) is the most famous (and most demonized) of the phytocannabinoids, it is also the most commonly occurring in the cannabis plant and the one with the most mis- or disinformation surrounding it. Tetrahydrocannabinolic acid, or THCA, is the acidic precursor to THC and has no psychoactive effects (Ameur, Haddou, Derrriche, Canselier, & Gourdon, 2013). Interestingly, THCA shares a co-dominant allele with CBDA during production (Russo, 2011). THC is converted to the active form of its precursor THCA in the same manner as most of the other phytocannabinoids: through decarboxylation via heat, or combustion (Nahtigal et al., 2016).

Yet it is a fact that THC is most known for its “psychoactivity.” This is a term most people struggle to understand; even many medical professionals know only its precursory meaning. According to the WHO, a psychoactive substance is one that, when administered to a patient, works on mental cognition or affects mental cognition; “psychotropic” is another term that is analogous to “psychoactive” (World Health Organization, 2019).

Psychoactive drugs fall into five categories:

1) sedatives and hypnotics

2) stimulants

3) opiates

4) hallucinogens

5) other

Cannabis falls squarely into the "other" category, as it exhibits properties from almost all of the categories (Biology Reference, 2019). It should be noted that many commonly prescribed medications can be classified as psychoactive; for example, a medication like metoprolol is considered relatively benign, despite its potential to affect cognition. THC, because of the endocannabinoid system's unique property of being a focused, systemic homeostasis, can at any given time exert symptoms from any of these categories based on the body's homeostatic needs. (Nahtigal et al., 2016).

Outside this well-known and studied attribute of THC, it has other less known medical benefits. These benefits include potent analgesic, muscle relaxing, antispasmodic, antiemetic, bronchodilatory, neuroprotective and antioxidant, anti-tumor, and antipruritic effects (Sinclair, 2016; Russo, 2011). THC is also a very effective anti-inflammatory with 20 times the power of aspirin and double that of hydrocortisone (Russo, 2011).

Cannabidiol (CBD)

CBD, or cannabidiol, is the second most commonly occurring of the phytocannabinoids in all hemp and most medicinal chemovars (Russo, 2011), which refers to a scientific profile of potency and presence of cannabinoids, terpenes, and biomolecules such as waxes and lipids ("Cultivar v. Chemovar: Debating the Debasement of Cannabis Vernacular - Terpenes and Testing Magazine," 2018).

CBD has a wide range of pharmacologic effects, with one of the more exciting being that of a modulator of THC through antagonism of the CB1 receptors (Russo, 2011). Through this action, the psychoactivity, or "high," associated with THC can be somewhat reduced and managed (Sinclair, 2016). This is of clinical utility when a patient has used more than a proper dose for themselves and needs a reduction of effects: CBD can be added to the patient's regiment and taken to help mitigate these unwanted side effects caused by too large a dose of THC.

Outside the modulation of psychoactivity, CBD also helps to control other potential THC-caused side effects like anxiety, tachycardia, hunger, and sedation (Russo, 2011). Other important effects of CBD include pain reduction, neuroprotection, antioxidant, cancer cytotoxicity, antiproliferation, antiemetic, anticonvulsant, and muscle relaxant (Russo, 2011).

Cannabichromene (CBC)

CBC, or cannabichromene, is a less-studied cannabinoid, although it is one that shows great promise. It has been shown to have antibiotic, antiinflammatory, antifungal, analgesic, antitumor, and anti-proliferative effects (Sinclair, 2016). Interestingly, CBC also exhibits modulatory effects against THC (Russo, 2011). Other medical benefits of CBC include gastric regulation, acne (MD5) control, and the reduction of intraocular pressure (Nahtigal et al., 2016).

THCV & CBDV

There are two propyl analogues of other phytocannabinoids, THCV and CBDV (Russo, 2011). The first of these is THCV, which is able to help regulate THC intoxication (Russo, 2011). Two of the more interesting medical effects of THCV are weight-loss and insulin regulation (Russo, 2011) (Nahtigal et al., 2016). Other pharmacologic effects include antiinflammatory, anti-nociceptive, anti-seizure, and a reduction of hyper-algesic states (Russo, 2011; Nahtigal et al., 2016).

The second of the propyl analogue phytocannabinoids is CBDV. This is a vastly understudied phytocannabinoid, as after its initial discovery in 1969, it was essentially shelved without further investigation until more recently (Russo, 2011). Despite this delay in research, CBDV has proven to be antiemetic, anticonvulsant, and anti-acne, among other benefits (Russo, 2011; Nahtigal et al., 2016).

AGED PHYTOCANNABINOIDS

Cannabinol (CBN)

Cannabinol, or CBN, is an oddity among the phytocannabinoids in that it is not decarboxylated through either heat or combustion, but rather through the oxidation that occurs through natural aging (Bow & Rimoldi, 2016; Russo, 2011). In other words, it is the oxidative byproduct of THC degrading over time (Russo, 2011).

CBN has been shown to have clinical benefits including analgesic, anticonvulsant, anti-inflammatory, antibacterial (specifically against MRSA), anti-proliferative, and anti-tumor effects (Russo, 2011; Nahtigal et al., 2016). It has also been shown that, by itself, CBN has almost no sedating effects, but when used in conjunction with THC has very strong

sedative effects (Russo, 2011).

Cannabigerol (CBG)

Cannabigerol (CBG), like the other aged phytocannabinoids, is derived from CBGA (Nahtigal et al., 2016). It is a weak partial agonist of both the CB1 and CB2 receptors (Russo, 2011). Medical effects of CBG include muscle relaxant, analgesic, antifungal, antitumor, mildly antihypertensive, antiproliferative, antibiotic, and antidepressant effects (Russo, 2011; Sinclair, 2016).

PHYTOCANNABINOID SYNERGY

The effects of many of these phytocannabinoids are perpetuated through the addition of other phytocannabinoids. In pharmacology, this is referred to as synergy or synergism, meaning that the combined effect of two or more substances is greater than the sum of their separate effects (Arcangelo, Peterson, Wilbur, & Reinhold, 2017).

In studies, phytocannabinoids have shown this synergism with the addition of each additional cannabinoid, causing a new term to be coined: "the entourage effect" (Nahtigal et al., 2016). The entourage effect refers to the synergism between these stacked cannabinoids, and is not actually limited only to cannabinoids—it also includes the therapeutic effect of terpenoids (Pellati et al., 2018; Nahtigal et al., 2016). One interesting aspect of the entourage effect is that of modulation. Through the synergistic and homeostatic effects, the collective group of phytocannabinoids (and terpenoids) will not let one exert too much or too little effect (Nahtigal et al., 2016). This is another factor showing the overall homeostatic effects of this medication.

The body produces endocannabinoids, and the cannabis plant produces phytocannabinoids. Together, both endo- and phytocannabinoids positively impact the body in aiding the achievement of homeostasis. Yet while there are various types of phytocannabinoids that work together, these are just one side of the coin. The next chapter will cover the other side, terpenes.

Chapter 7

TERPENES

> "Unique chemical abundances of specific terpenoids are predicted to be associated with chemotypes and species-level taxa. As the aroma of the plant is largely the result of the terpenoid composition, human selections for this plant may have been based in part on the monoterpenoid- and sesquiterpenoid-based aroma and on the cannabinoid psychoactivity."
>
> —(RICHINS, RODRIGUEZ-URIBE, LOWE, FERRAL, & O'CONNELL, 2018)

The cannabis plant is well known for its unique, recognizable, and at times pungent odor. The smell of the cannabis plant is caused by an abundance of a variety of chemical composites called terpenes, which are a group of essential oil compounds.

Terpenes have seen extensive investigation, especially in Eastern medicine, and have mostly been approved by the FDA as safe in numerous products (Russo, 2011), though the FDA continually issues warning letters to companies that make bold claims about their products that have yet to be clinically proven. There has also been significant research performed into the effectiveness of terpenes in various applications such as aromatherapy, topicals, and phytotherapy.

In recent decades, more significant studies have shown that the use of terpenes in a variety of ways can be a great complementary or alternative

treatment option for patients with a number of conditions. Terpenes in plant species, when present at levels greater than 0.05%, are of pharmacological interest because they are “lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled receptors, second messenger systems and enzymes” (Russo, 2011). Testing of various strains of medical cannabis in New Mexico, for example, found up to 19 different terpenoids with a content ranging between 0.06% and 3.3% in a large sample group (Richins, Rodriguez-Uribe, Lowe, Ferral, & O’Connell, 2018). Although there is a greater occurrence of phytocannabinoids in the plant (Richins et al., 2018), the terpenes found in cannabis seem to be one of the major components in its medicinal value.

DEFINING TERPENES

Broken down into simplest terms, terpenes are essential oils found in all plants and are the most abundant secondary plant metabolite (Dabrowski & Skarjda, 2017; Abbas et al., 2017). Numerous terpenes have been studied by the cosmetic, chemical, and food industries with many applications having been found (Abbas et al., 2017). More than 40,000 individual compounds fall under the classification of “terpene” (Abbas et al., 2017).

In terms of terpenes in cannabis, there have been more than 200 different terpenoids (organic, naturally occurring extra functional group on a terpene) found in the cannabis plant, with 140 terpenoids specifically “fingerprinted” for terpenoid make-up, allowing for easier identification of different cultivars (Nahtigal et al., 2016). The effects of the majority of the terpenoids found in cannabis remain un-researched at this point (Nahtigal et al., 2016); however, there are around 17 terpenoids that occur commonly in cannabis (Giese, Lewis, Giese, & Smith, 2015). Interestingly, while being part of the medicinal power of the cannabis plant, terpenoids constitute only a small part of the overall medicine contained in the plant. For perspective, cannabinoid concentration ranges between 0.1% to 40% of the dry weight of the plant (Giese et al., 2015). The total terpenoid content of the plant ranges from 0.01% to 1.5% of the dry weight (Giese et al., 2015). This is important to know as it has been found that any terpenoid content that is greater than 0.05% is of pharmacological interest (Russo, 2011).

Terpenes are biosynthetic compounds, the building material within

organic compounds (Nahtigal et al., 2016). Terpene tends to be a catch-all term for all terpenoids, but there is a difference. The difference between the two terms is that terpenes are hydrocarbons with extra functional groups (such as oxygen moieties or branching methyl groups) (Nahtigal et al., 2016), and terpene synthases or cyclases are the precursors to more complex terpenoids (Rehman, Hanif, Mushtaq, & Al-Sadi, 2016).

Terpenoids

When terpenes are altered structurally or chemically, the result is referred to as a terpenoid (Nahtigal et al., 2016). There is also a category of terpenoid called "volatile terpenoids" (such as mono, sesqui, and diterpenes) that make up the largest class of plant volatile compounds (Abbas et al., 2016). The number of isoprene units in a terpene determine its classification as a hemiterpene (one unit), monoterpene (two units), sesquiterpene (three units), diterpenes (four units), triterpenes (six units), and tetraterpene (eight units) (Rehman, Hanif, Mushtaq, & Al-Sadi, 2016).

Medical Effects

Terpenes themselves exert certain medical effects that can be added to each other to form a terpenoid entourage effect (Rehman et al., 2016).

This ability has added to the argument that whole plants are better medications than singular plant-derived compounds (Nahtigal et al., 2016).

Terpenes interact with cannabinoids through four different means:

1) Through a multi-target physiologic effect
2) Pharmacokinetics
3) Bacterial resistance
4) Side-effect modulation

Through this interaction, a combined entourage effect is noted, with the terpenoid and cannabinoid entourage effects adding to the other, further potentiating the effects of this medication and showing that the cannabinoid-terpenoid compound is the true medicine of the cannabis plant (McPartland & Russo, 2001).

The effects of terpenoids are exerted at multiple places in the body, including critical enzyme levels, neurotransmitter levels, G-protein receptors, and through second-messenger enzymes and systems (Nahtigal et al., 2016). Terpenes have an extremely high bioavailability due to their

lipophilic nature, which allows for them to easily and passively diffuse across membranes—including the blood-brain barrier (Nahtigal et al., 2016). The effects of many of the individual terpenes found in the cannabis plant will be discussed in the following sections.

MONOTERPENES

Limonene

Limonene is commonly found in many citrus fruits and has been associated with a number of health benefits. This is one of the most studied terpenes, as it is regularly used by cosmetic, chemical, and food companies (McPartland & Russo, 2001). It is a powerful anti-inflammatory and has potential anti-tumor effects as well (McPartland & Russo, 2001). It is currently being studied for the anti-tumor and anti-proliferative effects that it exhibits, particularly in the case of breast cancer (McPartland & Russo, 2001). Limonene has been shown to protect against aflatoxin B1 cancers through the restriction of liver conversion of pro mutagens to their active forms (McPartland & Russo, 2001). It is also a documented anti-anxiety and antidepressant and has been shown to reduce or remove the need for antidepressants (McPartland & Russo, 2001). Anti-fungal, anti-bacterial, and cellular regenerative effects have also been exhibited by limonene (McPartland & Russo, 2001), as well as gastroprotective and anti-spasmodic properties. Of important note, limonene blocks the development of cancer caused by benz(a)anthracene, which is the end result of cannabis combustion and the cause of the trademark “tar” (McPartland & Russo, 2001). Limonene may even provide natural protection against the inhalation of carcinogens that accompanies combusted cannabis (McPartland & Russo, 2001).

Linalool

Linalool is associated with the smell of lavender because it is abundant in the lavender plant. This terpene makes up five percent or less of cannabis oil and is considered a “minor” terpene despite being associated with some major health effects (McPartland & Russo, 2001). It has been well-documented as having sedative and calming effects, which are associated with its anti-anxiety properties. This is a total body effect, which not only reduces stress and anxiety through its sedative effects but also through reducing the stress hormone cortisol through direct effect exerted on the hypothalamic-pituitary-adrenal axis (HPA) (McPartland & Russo, 2001).

The action of linalool on the HPA has also been shown to boost immunity through overall stress reduction and the resulting cortisol drop (McPartland & Russo, 2001). Linalool has even been demonstrated to serve as an anticonvulsant, analgesic, and as potentially inhibitory of cancer cell proliferation. Linalool has also been shown to help mitigate the psychoactivity of THC (McPartland & Russo, 2001).

Pinene

Pinene, a bicyclic monoterpenoid that comes in alpha and beta forms, is associated with the fragrance of pine, is the most common terpene found in a natural environment, and is the most common naturally occurring terpene on Earth (McPartland & Russo, 2001). It has been used medically for millennia (McPartland & Russo, 2001). It is known to have major anti-inflammatory and anti-bacterial effects, with efficacy against *Staph Aureus, S. epidermidis,* and *Propionibacterium Areus.* It also has gastroprotective and anxiolytic effects. Pinene is cytotoxic in vitro against human hepatocellular carcinoma and human melanoma (McPartland & Russo, 2001). Pinene has been shown to be a bronchodilator with effects showing even in asthmatics with the inhalation of combusted cannabis (McPartland & Russo, 2001).

Myrcene

Myrcene is found in hops, lemongrass, and mangoes, which are documented to be naturally anti-inflammatory, and works similarly to cannabinoids in blocking prostaglandins as well as having antioxidant properties (Shah, 2010). Myrcene exerts its analgesic effects on the same receptors that are antagonized by naloxone, which allows myrcene to have potent anti-spasmodic, muscle relaxing, and analgesic effects. In addition to the aforementioned effects, myrcene is also antipsychotic and possibly inhibits proliferation of cancer (McPartland & Russo, 2001).

Of interest to note with myrcene is its concentration effects. The sedation effects of this terpenoid are dependent upon the percentage contained in the cannabis strain. To this point, strains with myrcene content of less than 0.3% will exhibit *C. Sativa-like* effects (more energetic) whereas strains containing more than 0.3% will exert a more *C. Indica-like* effect causing sedation (McPartland & Russo, 2001).

Terpinolene

Terpinolene is found mostly in flowers and exhibits a sweet, herbal, and floral smell (McPartland & Russo, 2001). This terpene is an antidepressant

and sedative, causing CNS depression and providing sedative and hypnotic effects, and has shown benefit as an anti-proliferative against many forms of cancer (McPartland & Russo, 2001).

Borneol

Borneol is associated with minty and herbal scents. It is used as a natural insect repellant and has anti-inflammatory properties (McPartland & Russo, 2001). Borneol has also been shown to have anti-fibrosis effects, decreasing the fibrotic results of wound healing. Another effect is that, similar to myrcene, borneol causes increased cell permeability allowing for an increase in overall cannabinoid absorption and effect (McPartland & Russo, 2001).

The largest effect of borneol is its powerful antifungal and antibacterial activity. In fact, it has been found to be 98% effective against otitis media; this is more effective than neomycin with a better safety profile (McPartland & Russo, 2001).

Octanol

Octanol is one of the primary terpenes found in frankincense. It has strong anti-inflammatory and analgesic effects. This terpene exerts a very strong anti-inflammatory entourage effect when used in conjunction with pinene and linalool; it also inhibits the overexpression of COX 2, which is the precursor to prostaglandins. The overall effect of this inhibition is a dramatic drop in inflammation (Kim, Cho, & Jang, 2019).

Terpineol

Terpineol is a floral smelling monoterpene found in lilacs (McPartland & Russo, 2001). This terpene has been shown to have sedating and anxiolytic effects similar to A-pinene and is an excellent adjunct for patients who suffer from insomnia, as it has shown sedation effects and reduced motility in mouse studies (McPartland & Russo, 2001). Terpineol is also an anti-oxidant, anti-microbial, anti-fungal, and antibiotic with effects on *S. Areus, S Epideridis, Propioni Bacterium* acne, *Pseudomonas*, and *Plasmodium Falciparum* (McPartland & Russo, 2001).

Cineole

Cineole is found in eucalyptus and has a menthol-like scent (Kim, Cho, & Jang, 2019). This terpene is anti-lnflammatory anti-oxidant, and analgesic with effects benefiting patients with neuropathic pain. Of interesting note, cineole exerts an anti-edematogenic effect, which has many potential

medical applications and is currently being further researched (Kim, Cho, & Jang, 2019).

Ocimene

Ocimene is an herbal- and woody-smelling terpene and is one of the terpenes found in basil. As with many of the other terpenes, it is both antimicrobial and antifungal (McPartland & Russo, 2001). The most interesting attribute of ocimene is that it is also a decongestant: it can allow patients to expel phlegm and mucus more easily (McPartland & Russo, 2001).

Cymene

Cymene is a spicy smelling terpene that is found in cumin and thyme (Kim, Cho, & Jang, 2019). There are massive analgesic effects associated with this terpene, referred to as an "anti-hyper algesic," as well as potent anti-lnflammatory effects (Kim, Cho, & Jang, 2019). Research points to anti-cancer benefits from cymene, but as with many of the other terpenoids, much more research is needed (Kim, Cho, & Jang, 2019).

SESQUITERPENES

Beta-Caryophyllene

Beta-caryophyllene can be found in a variety of spices including black pepper, cinnamon, oregano, and it has been documented for several therapeutic effects. It is gastroprotective and has shown benefit without a reduction in gastric acid or pepsin secretion (McPartland & Russo, 2001). The anti-inflammatory effects that this terpene exerts are very strong, comparable to phenylbutazone; it also has potent anti-fungal and analgesic effects (McPartland & Russo, 2001).

Beta-caryophyllene is one of the few terpenoids that directly interacts with the endocannabinoid system and has been demonstrated as a neuroprotectant by activating CB2 receptors and acting through the PPARy pathway (Bento et al., 2011; Kim, Cho, & Jang, 2019). In addition, as the most abundant naturally occurring sesquiterpene, it also causes a reduction in vascular permeability (McPartland & Russo, 2001).

Humulene

Humulene (Alpha Caryophyllene) is a musty- and hoppy-smelling terpene that is closely related to beta-caryophyllene (McPartland & Russo, 2001).

This terpene has been linked to strong anti-inflammatory and analgesic effects, as well as anorectic effects which may make this terpene beneficial for patients looking to control their appetite or lose weight (McPartland & Russo, 2001). Humulene is also antibiotic and anti-fungal, like many other terpenes (McPartland & Russo, 2001).

Valencene

Valencene is a woody- or citrusy-smelling terpene that is found in oranges and grapefruits (McPartland & Russo, 2001). There is not much currently known about valencene other than it is a potent antiinflammatory and that it has been shown to improve the efficacy of cancer drugs (McPartland & Russo, 2001). More research is certainly needed into this terpenoid.

The relationship between terpenes, phytocannabinoids, and the endocannabinoid system is complex. Though there has been research into the subject of terpenes and their entourage effect with phytocannabinoids and endocannabinoids, much more is needed to discover the significance and impact terpenes have in the deep relationship between cannabis and the human body. Yet even as researchers work to unravel the effects of the many active chemicals in cannabis, pharmaceutical companies have begun patenting and selling synthetic versions of them. In the next chapter, we will examine their latest efforts, and the potential risks and rewards inherent in their use.

Chapter 8

SYNTHETIC CANNABINOIDS

> "It is important as we move forward in creating synthetic cannabinoids or modulators of the endocannabinoid system that are farther and farther away from the natural compounds produced by plants or the body that we make sure side effects both short-term and long-term are minimized."
>
> —Ross, 2018, p.p. 44

No medical discussion of cannabis could be complete without addressing the subject of synthetic cannabinoids. Currently, synthetic cannabinoids are found in several different forms, the most common being Marinol (drobabinol), Cesamet (nabilone), Sativex (naviximols), and Epidiolex (Mintz et al. 2015). The difference between these pharmaceuticals and whole-plant cannabis is that pharmaceuticals are comprised of a single unopposed cannabinoid (like THC in Marinol) or a combination of two, as in Sativex (THC and CBD).

Though these synthetics have shown some promise, they have yet to demonstrate the same level of effectiveness as the actual cannabis plant, for one particular reason.

SYNTHETICS LACK SYNERGY

The problem with pharmaceutical cannabinoids is the loss of the entourage

effect and thus the loss of the overall potency of the cannabinoidterpenoid compound. This problem can be broken down into three levels:

1. The isolation of a cannabinoid from others removes much of the compound's therapeutic value through the exclusion of other cannabinoids and terpenoids. This exclusion removes the entourage effect, which enhances the medical effect of cannabinoids (Russo, 2011).
2. Isolating cannabinoids causes unrestrained effect. This unmitigated effect can lead to an excessive effect, especially in the case of THC. A side effect of this can be increased levels of anxiety that many patients find unbearable. (A familiar example of this type of side effect would be the cough that is associated with Lisinopril (Lexicomp, 2019). This side effect does not mean that the medication is not having the desired effect; however, the side effect greatly reduces the patient's quality of life, making the therapeutic effect of the medication not worth the alterations in lifestyle. Most other phytocannabinoids have the effect of restraining the psychoactive effects of THC (Russo, 2011). Another example of unrestrained and synthetic cannabinoids is the case of Rimonabant. Rimonabant was a synthetic isolate of CBN that was used as a diet drug in Europe with great success, except for the side effects. Rimonabant was associated with mood alterations in up to 10% and suicidal ideation in more than 1% of users, *even if they had never previously experienced suicidal thoughts* (BBC News, 2007). Due to these side effects, Rimonabant was never approved for use in the United States.
3. Synthetic cannabinoids are more concentrated and stronger than naturally occurring cannabinoids, which means that they will have stronger effects. Combine this with the unrestrained effect that they have without other cannabinoids present to mitigate their effects, and the intended therapeutic effects of these medications is somewhat hard to achieve without the aforementioned side effects that most patients cannot tolerate.

WELL-KNOWN SYNTHETICS

Marinol

Marinol (dronabinol) is a synthetic of A9-tetrahydrocannabinol (THC), the most studied of the phytocannabinoids, and uses as its mechanism of action an unopposed activation of CB1 and CB2 receptors (Lexicomp, 2019). Marinol comes in capsules that contain a sesame oil carrier and range in strength from 2.5 mg to 10 mg (an oral solution is also available in a 5 mg/ml concentration).

There are serious psychiatric side effects to Marinol, including paranoia, delusions, and worsening of mania, depression, and schizophrenia (RX List, 2017). This is due to the unrestrained effects of THC and shows the body's need for the other phytocannabinoids to help rein in these psychoactive effects. Many of the psychiatric side effects (anxiety and paranoia in particular) are too much for patients to tolerate and cause them to discontinue the use of this medication, even if the desired therapeutic effects are being achieved (RX List, 2017).

Cesamet

Cesamet (Nabilone) is another a synthetic form of THC. Cesamet comes in 1 mg capsules. The safety profile of this medication is very similar to that of Marinol, including the same type of psychiatric side effects (Lexicomp, 2019; RX List, 2017). Again, many patients have difficulty dealing with these side effects and discontinue the use of this medication.

Sativex

Sativex is slightly better tolerated than the previous two medications discussed due to the make-up of the medication: it is comprised of Δ9-tetrahydrocannabinol (THC) and CBD (cannabidiol) together in a 1:1 ratio. This ratio helps to make the psychoactive effects of THC more tolerable (GW Pharmaceuticals, n.d.).

Despite the improved tolerability of this medication, it still has a laundry list of adverse effects (Lexicomp, 2019). The reason this medication has more side effects than whole-plant cannabis may be due to the lack of an entourage effect from other phytocannabinoids and terpenoids. Without these compounds to moderate the effects, Sativex falls short of whole-plant cannabis' effects.

Epidiolex

Epidiolex is the newest of these medications, having been approved by the FDA in June 2018 (Lexicomp, 2019). This medication is a pharmaceutical concentrate of cannabidiol (CBD) oil and uses purified CBD—which is great—but CBD, while it avoids the adverse effects of other synthetics, is

still missing out on the entourage effect provided by the other cannabinoids (GW Pharmaceuticals, n.d.). Epidiolex also has seizures as one of its side effects, while being a medication for seizure control.

The other problem with this medication is the cost. The average cost of one 1ml bottle of oral solution containing 100mg is more than $1,200 (Good RX, n.d.), with a year's supply costing more than $30,000 (Loftus, 2018). This medication is currently only approved for a rare form of childhood epilepsy known as Dravet syndrome (Lexicomp, 2019). Another worthwhile note about the cost: a similar amount of medical grade, whole-plant CBD tincture, which actually works better for the treatment of seizures, costs roughly $1,200 for a year's supply.

Spice

Spice is the most dangerous (and surprisingly legal) synthetic cannabinoid on this list. It is a concentrated synthetic isolate of Δ9-THC that can be bought at gas stations, smoke shops, or "head shops" where it is known as "spice" or by brand names like K2 (National Institute on Drug Abuse [NIDA], 2018).

The problem with this "legal" synthetic is that it is intended for the sole purpose of causing psychoactive effects, or a "trip" (NIDA, 2018). This causes many unwanted side effects due to the concentrated effects of the synthetic cannabinoid, leading to extreme anxiety, confusion, paranoia, and hallucinations (NIDA, 2018). Another point of interest is that synthetic cannabinoids can be addictive, adding to the risk (NIDA, 2018).

Synthetic cannabinoid medication is an area that shows great promise and interest to many providers due to the specificity of dosing. Yet this is among the few scarce benefits of current synthetics, with their side effects and risks far outweighing the benefits in most cases. The safer alternative to these synthetics, namely whole plant natural cannabis, which has been used medically for millennia with the benefits well outweighing the risks. It would therefore seem more prudent to solve the issue of controlling whole-plant cannabis dosage, rather than creating potentially unbalanced synthetic derivatives.

Chapter 9

MEDICAL DOSING: A GUIDE FOR PROVIDERS

> "Here we have a group of compounds, an endogenous system of major importance, it is not being used as much as it should be in the clinic. It is of great promise in the clinic."
>
> —RAPHAEL MECHOULAM, *THE SCIENTIST*

The good news is that the use of medical cannabis is gaining more traction among healthcare professionals. More high-quality research is being published today than ever before, with many studies giving insight into just how cannabis can help patients better manage their health. Coupled with higher safety profiles and a lower risk of addiction than traditional pharmaceuticals, medical cannabis is becoming more popular among patients and medical practitioners alike.

Yet many physicians understandably have questions about medical cannabis dosing. Studies have shown that most medical students and healthcare providers agree they lack the knowledge necessary to properly recommend cannabis to their patients (Karanges, 2018). Only a handful of medical schools offer classes on cannabis, and there is very little guidance on how practitioners should move forward with cannabis therapy.

This leads most healthcare providers to ask the same question: How do you discover the right dose for an individual patient?

There is no one-size-fits all answer, either. Many different factors affect medical cannabis dosing, including the strain (specific

phytocannabinoid and terpenoid makeup), the condition being treated (as some conditions such as chronic pain require higher THC content as well as more frequent dosing), and the individual patient (there are genetic differences between individuals ECS makeup and needs). However, by properly considering the patient profile, providers are able to make better recommendations for cannabis therapies.

CBD THERAPiES

Providers have become less resistant to products that contain CBD alone now that it is legal in most states, with many of their patients currently purchasing products with numerous beneficial effects on the open market. Pharmaceutical companies are also formulating CBD oils for specific epileptic conditions. Yet while many of these products can be positive for consumers, there are several common misconceptions surrounding CBD products that confuse the average layperson.

For example: almost all CBD products contain THC, and many states regulate the level of allowable THC in legal CBD products. In fact, one of the main selling points for CBD products is that they do not have enough THC to be considered psychoactive, a term many consumers have come to misunderstand in relation to cannabis. Many pharmaceutical products available over-the-counter *are* in fact psychoactive, and provide warnings against operating machinery while under the influence thereof, but the average consumer fails to correlate that the psychoactivity of cannabis is actually directly comparable to these kinds of medications. Furthermore, while CBD products do have the advantage of being minimally psychoactive, they lack the entourage effect provided by the combination of cannabinoids found in whole-plant products.

In addition, all CBD products are not created and formulated to an equivalent standard. There are a host of products on the open market today, especially those found at gas stations, flea markets, and on websites that claim to be of the highest quality, yet. many of these low-priced products are in no way intended to improve the health of those that take them. An informed consumer should research CBD products with the same amount of consideration they would for other medications in their homes. There are numerous CBD producers and distributors that are highly reputable, and through independent research, an average consumer should be able to quickly find a good source for high-quality CBD therapies.

CBD Therapies in Special Populations

High CBD therapies are exceptionally effective for special populations that might otherwise experience adverse effects from a psychoactive substance. The strains of cannabis that are particularly high in CBD are now cultivated primarily because of their effectiveness in therapy for children and because of their lack of psychoactive effects. The first well-known strain, "Charlotte's Web", was originally very disappointing to recreational marijuana cultivators who were primarily focused on increasing THC content (Young, 2013); it is only in the last decade or so that researchers have been able to fully test cannabinoids in plants and focus on the effects of the specific cannabinoids in various strains. For example, the effectiveness of CBD oils on epileptic conditions such as Dravet syndrome is relatively new; however, the results seen so far are tremendous (Pickert, 2014). With the use of natural CBD therapies, most symptoms are eliminated, even in patients experiencing hundreds of seizures each day (Young, 2013).

Patient Research

As patients research available CBD products for personal use, it is very important to look over lab testing, ingredients, and any reviews available. The best CBD products can be ordered through trusted online retailers; however, many local CBD stores and dispensaries serve as good sources for information and reliable products as well. For this reason, the best advice that a provider can offer a patient seeking CBD-derived products is often to consider their purchase as they might other nutritional or supplemental products. (Most patients would not purchase a multivitamin at a gas station or at a tobacco store.)

Although CBD therapies seem new, they have tremendous potential when properly formulated. As further knowledge is gained regarding the effectiveness of cannabinoid therapies, more health-related products containing high-CBD formulas will reach the market and could become the primary recommended therapeutics for the management of numerous symptoms.

PSYCHOACTIVITY AND DOSING

While there are many pieces to bear in mind for providers considering cannabis, most would agree that their largest hesitation is the associated psychoactivity. The term "psychoactive" has become quite common in the

language describing numerous medical products available over-the-counter; however, when used in reference to cannabis most people do not fully understand what is meant. Clearly stated, psychoactive means "affecting the mind or behavior" (Merriam-Webster, 2019, p. 1), but when this term is used in the discussion of cannabis it seems to be often exaggerated. Commonly, the psychoactive effects of cannabis tend to be represented and discussed in the language of hallucinogens, be it in popular culture, the media, or in schools. In reality, the term psychoactive could be descriptive of a substance, a habit, or even a belief—anything which can affect someone's mind or behavior is covered under the definition of the term. Substances that are thought of as relatively "benign" like caffeine and sugar—these are psychoactive. Many medications that providers frequently prescribe fall into this category as well.

A recent *Scientific American* article noted that 1 in 6 Americans are on psychoactive, psychiatric medications (Miller, 2016)—and these are just the patients that admit to taking them. Mind and behavior-altering substances should never be taken lightly, and this includes cannabis products; however, many patients are in need of a better understanding of the *level* of psychoactivity they should expect from therapeutic doses of THC.

Properly dosed medical cannabis can best be compared to one of the most common pharmaceutical products available in the pharmacy today, Benadryl. A common practice is to prescribe 25—50 mg of Benadryl for pre-procedural sedation. The reason for this is the calming and antianxiety effects that this medication produces through its psychoactive properties. In much the same manner, the psychoactive effects of properly dosed cannabis serve a similar purpose. For most novice patients, this effect is achieved via a dose of cannabis equivalent to roughly 5 mg, taken through an oral or inhaled route, and which provides a very similar calming and anti-anxiety effect. Considering this comparison and the safety profile of cannabis, the truth becomes clear: psychoactivity in properly dosed cannabis is a less significant concern than many providers might at first think.

THE DIFFIOULTY OF CANNABIS DOSING

Yet it is true that medical cannabis isn't like other medications providers typically recommend to their patients. Most medications are prescribed with a particular dosage, which is often based on the patient's age, sex,

height, weight, and medical condition. These factors *are* all considered in the dosing of medical cannabis, but the relationship isn't quite as linear. With cannabis, some patients experience great effects with a relatively low dose (Wilsey et al., 2013), while other patients will need higher dosages to find similar symptom relief. When this is combined with the number of strains, methods of ingestion, and a patient's condition and medical history, the situation is further complicated. Practitioners should take into account a few considerations when addressing how cannabis will impact their patient and his or her condition.

The first aspect to be addressed is the market climate in the patient's current locale. Is the market medical only, medical and recreational, or completely restricted? This is important to consider as it influences the legality of the medication and the patient's acquisition thereof; the quality of the medication; the price of the medication; and the safety and efficacy of the medication. Legality is important to consider because in states where a patient must seek cannabis through the black market, there is an added risk of physical or legal duress. Patients, when being counseled as to risk versus benefit for this medication, should also be counseled on the legality in their area in a non-judgmental way.

The legality of the medication will also typically affect the quality, with legal areas having access to purer "medical grade" cannabis and restricted areas being reduced to whatever they can find, which can result in low-quality medication, what is known colloquially as "schwag" or "skunk weed." Currently, medical and legal cannabis contains roughly between 15% and 30% THC (with most strains averaging around 20%) and CBD content between trace amounts and 15% with the average content being between 1% and 5%.

The locale also will affect the price of the medication. If there are restrictions, black market demand will in turn drive up the cost. The inverse is also true: in places like Oregon, where cannabis is both medically and recreationally legal, cannabis prices have plummeted due to over-proliferation of the market. The average price of medical grade can nabis nationally ranges between $4—10 per gram; in Oregon, the price has dropped to around $2 per gram.

The final consideration regarding location is the safety and efficacy of the medication to which a patient has access. While cannabis is legal in some capacity in the majority of states, there are still many states where it *is* illegal, causing a thriving black market where patients are unsure what medication they are actually getting.

REGULATED MARKETS

Even in states where cannabis is legal to varying degrees, there are tight restrictions on grows, or facilities where cannabis is grown, including the types of nutrients and pesticides that can be used. These facilities are comparable to medication manufacturing facilities, requiring clean rooms, sterilization processes, and manufacturing standards. These kinds of regulations are of the utmost importance due to cannabis behavior as a soil cleanser. The cannabis plant has been used for millennia by farmers as a soil detoxifier because it absorbs toxins from the soil, but the result of this absorption is an accumulation of toxins in the bud/flower of the plant, which in turn poses potential risk to the patient.

One such risk is the often-mentioned cannabis hyperemesis syndrome. This syndrome has been linked to high levels of cannabis consumption, but when observed more closely, this syndrome is most likely related to neem poisoning. Neem oil, which comes from the neem plant, a type of evergreen tree native to India, is often used as a "natural" pesticide. Though neem oil poisoning is rare in adults, symptoms include seizures, vomiting, toxic encephalopathy, and metabolic acidosis (Mishra & Dave, 2013). Cannabis hyperemesis syndrome, though also rare, causes severe vomiting, nausea, dehydration, and weight loss, seeming to mimic neem poisoning to the letter ("Articles," n.d.).

Medical vs. Recreational Cannabis

Whether cannabis usage should be classified as medical or recreational is a common debate, with many critics of recreational cannabis use equating the practice to the consumption of alcohol. Yet this stance could not be further from the truth.

The consumption of alcohol, especially in excess, is used by many people to self-medicate for various reasons including social anxiety, depression, insomnia, and many other conditions. There may be some individuals that use cannabis in the same way, and do so in excess. However, unlike alcohol, which is dangerous, can be lethal, and only numbs symptoms, cannabis and its phytocannabinoids are not lethal in excess and work on the cannabinoid receptors, bringing about homeostasis and symptom relief within the body. Therefore, it

can be argued that all cannabis use is medical use, placing the importance of the debate where it should be, focused on what is best for the patient.

METABOLISM AND PHARMACOKINETICS OF CANNABIS

As with the discussion of any medication, pharmacokinetics are an important factor. In the discussion and examination of the pharmacokinetics of cannabis, there are many mechanisms that should be addressed, including absorption, distribution, metabolization and excretion. Absorption is dependent upon the form of cannabis used (inhaled/topical/edible) and how quickly the medication enters the bloodstream, as with any other medications (IV/oral/topical). Inhalation has an almost instantaneous absorption, while oral consumption can take an hour or more. THC and its metabolites are quickly distributed to fatty tissues and organs with large amounts of blood flow due to the lipophilic nature of these compounds, with the metabolism of THC accomplished primarily through the cytochrome P450 (CYP 450) system, the majority of which takes place in the liver (Klumpers & Thacker, 2019).

There is also some confusion in the literature as to cannabis's effects on the metabolization of other medications. The effects in the literature range from no effect on other medications to as much interaction as a daily glass of grapefruit juice with statins (Sinclair, 2016; Klumpers & Thacker, 2019). Due to this uncertainty of effect on other medications, the same cautions used for all other medications should be used here. For the provider, these interventions include using the smallest possible starting dose to mitigate interactions; evaluation of current medications for interactions; and using cannabis one to two hours after the medication in question.

The final step, excretion of cannabis, shows the body's need for cannabinoids, as the body so extensively uses THC that the amounts that leave the body unchanged are almost negligible (Klumpers & Thacker, 2019). The majority of phytocannabinoid metabolites are excreted in the feces, with the rest excreted in urine (Klumpers & Thacker, 2019).

PATIENT RECOMMENDED DOSE

DISCUSSION

To start the dosing conversation with patients, the first aspect of cannabis to be discussed is the difference in phenotypes. As mentioned previously, medical cannabis has three major phenotypes: *C. Sativa, C. Indica,* and hybrids. *C. Sativa* strains tend to be more energetic and uplifting, being associated with activity and daytime use. *C. Indica* strains are more physically sedating and are used for insomnia and relaxation. Hybrids are the result of breeding a *C. Indica* and *C. Sativa* strain together. However, hybrids are rarely a perfect "middle of the road " mix of the two, usually presenting with a "lean" toward one or the other (known as a *C.* Indica-dominant hybrid or a *C.* Sativa-dominant hybrid, respectively). These strains will exert effects that can be associated with both pheno types, and usually the effects will lean toward the dominant phenotype in the strain, sativa or Indica, when used.

The next consideration is the specific cannabinoids and terpenoids required to see benefit for the patient. In this, the patient's condition should be weighed against different cannabinoids to determine which type will be most effective. Doing so will help the patient in determining which cannabinoids they should be looking for when purchasing their medication. Terpenes should also be discussed with the patient to best understand which terpenoids will be most beneficial in the treatment of their condition. It is beneficial to remember that both phytocannabinoids and terpenes exert an entourage effect within their own specific group, and when combined, they exert an added entourage effect in conjunction with each other's groups. This combination of cannabinoid/terpenoid entourage effect shows the strength of the cannabinoid-terpenoid complex (CTC). The CTC should be part of evaluating any strain for effectiveness for individual patients.

EDUCATING THE PATIENT

The dosing specifics previously discussed provide helpful tools in educating patients in regards to how to choose their medication. These factors should be considered by the patients as well as they pick out a medication "strain" from their local dispensary. They should be able to ask the sales staff at their dispensary of choice about which strains will meet their individual needs based around this dosing assessment.

Note that many strains, even at medically-focused dispensaries, have somewhat comical names rooted in cannabis history and pop culture. Examples include: “Gorilla Glue,” “Blue Dream,” “Skywalker OG,” and “Purple Kush.” Some of these names refer cheekily to the result: Gorilla Glue, for example, is meant to “hit like a gorilla” and leave one “glued to the couch.” This particular strain of cannabis has medically been linked with stress reduction and treatment of insomnia.

EMPOWERING THE PATIENT

To empower a patient in the use of medical cannabis, a provider must first help facilitate the formation of a “patient-provider alliance”, a partnership in the management of their condition. The provider should approach this interaction in a non-judgmental manner in order to allow for an open and honest relationship with the patient. This is a new way of thinking about cannabis for most providers—as a medication rather than a drug. As such, there is a need to significantly shift the approach and mentality toward cannabis. A parallel example is one that perspective practitioners need to take with any information that contradicts what has been passing as truth for decades. For most providers, a change of thought process is required to approach any new patient community in a compassionate, understanding, and open manner. In the same light, cannabis changing from being an illegal and illicit substance to one of medical value will require many providers to reflect internally, challenge their own assumptions, and evaluate how they approach cannabis and their patient population.

One of the largest benefits of medical cannabis in its new role as an adjunct or primary treatment for patients is that of patient empowerment. For example, take a patient who is taking Percocet 5/325 mg, two tablets every four hours for post-surgical pain. This patient would be severely limited in what they could do to treat breakthrough pain, being restricted mostly to nonpharmacologic methods (ice, heat, rest, meditation, etc.). If this patient were to begin using cannabis as an adjunct or primary treatment, the patient could use oral cannabis (edibles or tinctures) for long-lasting pain control, inhaled cannabis for immediate breakthrough pain control (comparable in onset to intravenous medications), and/or topical cannabis for focused analgesia. The advantage of any form of this kind of usage is that it puts control into the patient’s hands. Doing so will lead to better symptom control and compliance. The patient has multiple avenues through which to treat their symptoms and can treat them with the

urgency required, leading to tighter symptom control.

MEDICATION PREPARATION METHODS

Patients who are seeking cannabis for medicinal purposes may have a variety of products to choose from, especially in states that have a medical and recreational market. When discussing cannabis, a healthcare provider must be aware of the legality of cannabis and cannabis-derived products at the state level because patients may seek treatment from the black market in states with restrictive legal atmospheres. Medical cannabis is currently available in a variety of forms with a host of derived products that can be consumed by methods of inhalation, ingestion, or dermal absorption.

There are a variety of products and methods from which a patient can choose for his or her personal condition and preference. The most well-known are inhalation products, including the dried flower of the cannabis plant and various forms of concentrate, which may be consumed through combustion or vaporization methods. Patients may also choose to ingest cannabis in the form of oil, tincture, food products, or beverages, among others. In areas with regulated cannabis markets, newly developed food products reach store shelves regularly, and patients should be advised to use caution with new consumables. In addition to the other forms, cannabis-based topicals are becoming common as well. With each method having a different onset time and level of potency, it is important that new patients be advised in the products and the consumption recommendations of each available type. This is because the metabolism of cannabinoids and endocannabinoids in the body differs significantly depending on the route of administration, as determined by its distribution into different tissues and the blood stream. It is therefore helpful for the clinician to approach this subject based on that route of administration. as the dose and therapeutic effect will vary due to different metabolic pathways.

INHALATION

Combustion

Smoking is the inhalation and exhalation of combusted dried cannabis flowers. There are a tremendous number of apparatuses that can be used to smoke cannabis. Most often, new users will smoke cannabis rolled into special paper; this method is known as a joint, but users may also elect to

use a pipe. There are several different types of pipes a patient may choose, though there are many common misconceptions surrounding which type is safest or most effective. Pipes might incorporate water or multiple chambers in which the smoke can decrease in temperature, resulting in more easily inhaled "hits." A hit is comparable to a single dose, commonly called a "puff" from an inhaler or nebulizer. Though the common perception among most cannabis users is that the filtration of carcinogens through water pipes make them a superior smoking method, there doesn't seem to be much measurable difference between joints or pipes of any kind. The only real benefit of using a pipe with a cooling method is what users describe as a "smoothing effect," which minimizes irritation of the lungs, thus reducing the amount of associated coughing.

Vaporization

Vaping (short for vaporizing) is the inhalation and exhalation of cannabis vapor that has been created without direct combustion. Vaporizers typically use a heating element to activate the compounds in dried cannabis flower or concentrates by heating them to between 300—400°F without causing them to combust, which occurs at 451°F (Rahn, 2016). Often, cannabis users will prefer vaporizers for their ease of use and lessened potential negative side effects ("Are Vaporizers the Safest Way to Smoke Weed?" n.d.).

Vaporizers come in a variety of shapes and sizes; however, most will have a chamber in which either dried cannabis flower or concentrates are inserted. Once the patient enables the device, it will heat the chamber creating vapor, which can be inhaled through an attached mouthpiece. These devices tend to provide more accurate methods of dosing, with many concentrate pens providing specific dosage (ex. 5 mg) for a "hit" lasting a specified length (ex. 5 seconds).

Onset and Duration

Inhalation methods are known to be rapid in onset and may have a limited duration, which can lead to multiple successive doses within a short time period to maintain a physiologically steady state. Duration of therapeutic effectiveness is variable and based on the specific phytocannabinoids and terpenes found in each strain, along with the individual patient's ECS and level of personal tolerance.

Maintaining Clean Tools

Smoking or vaporizing cannabis can leave a residue in glass pipes or vaporizers, and other forms of cannabis such as wax can build up and solidify. It is very important that any medicine be taken in the cleanest way possible. By using qQ-tips, alcohol and alcohol wipes, patients can easily clean pipes and mouthpieces. Vaporizers purchased through retailers typically come with cleaning and care instructions that are easy to follow.

Many glass pipes use water and other filtration techniques to remove plant matter that could be inadvertently inhaled with the smoke. It defeats the purpose, however, not to use fresh water, and it is essential to regularly clean the pipe and remove that filtered plant matter. While vaporization eliminates combustion from the process altogether, these devices also need to be regularly cleaned and the mouthpieces sanitized. Basic maintenance is very important to ensure that all of the tools and pieces are in their best condition. These basic steps of care will help users have a better experience with cannabis therapy.

INGESTION

Edibles are one of the more well-known secondary forms of cannabis dosing methods. As is commonly represented in popular culture, cannabis can be used to make food and drink items. Edibles come in many forms such as butter, candy, baked goods, soda, oils, and tinctures. Consumable products are very popular with new users because they seem to be the most comparable to other medications; however, a new cannabis user should be very cautious. In regulated medical cannabis markets, the amount of phytocannabinoid concentration is listed on the packaging and can help guide patients on the exact potency of the product. In states that only have black market products available, there is no way a patient can know the exact dosage level, and they will likely be unable to continually purchase the same products consistently.

Onset and Duration

Edible cannabis products are known to have the slowest rate of onset of any cannabis-derived good. This can be further lengthened if the patient has recently eaten, and in many cases results in the activity of phytocannabinoids and terpenoids having delayed activation during digestion. Edibles also have a much longer half-life than cannabis in other forms. The most significant new-patient problem with consumables is that the slow onset typically causes patients to consume more than necessary, which leads to undesirable effects. Patients should use caution around consumable items and should familiarize themselves with the effects by using a graduated dosing regimen.

A special consideration with edibles is their similar appearance to other baked goods, which puts pets, small children, and other family members at risk. Patients should be educated on these safety concerns and advised to store them safely away from other food items.

DERMAL ABSORPTION

Topicals and patches are becoming increasingly popular because of the milder and longer-lasting effect from dermal absorption. These cannabis products are applied directly to the skin and have a longer half-life than inhalation methods. The most significant factor in the efficacy of topicals and patches is whether a product contains a penetrating agent (such as peppermint) to enable better dermal absorption. The most exciting aspect of cannabis-based creams or ointments is that they can be directly applied to problem areas. Topicals are non-intoxicating and are easily applied to relieve conditions such as dermatitis, inflammation, cramps, aches, or pains. Transdermal patches, however, are formulated to penetrate deeper into the body and can cause intoxication by entering the bloodstream.

Onset and Duration

Dermal products usually act quickly, particularly when their formula includes a penetrating agent to increase absorption. The duration of therapeutic effect can vary greatly depending on the actual formula used in the topical or patch. While some creams may only be effective for an hour or so before reapplication, some patches advertise the ability to deliver effective therapy over a twelve-hour period.

THE SAFETY PROFILE AND SIDE EFFECTS

OF CANNABIS

It is important to understand the safety profile of any medication and cannabis is no exception. Healthcare providers and patients should include this topic as a part of the discussion on medical cannabis. While most often the use of cannabis is safer than many other pharmaceutical options, there are several known side effects that can impact each patient with a unique level of intensity.

Side effects of cannabis have been known to include psychotropic effects (altered color and time perception), anxiety, coughing, dry eyes and mouth, impaired memory, and altered thought processes.

There are two very important points to be made about the side effects of cannabis:

1. These side effects are all temporary and most, if they occur, are dose-dependent (caused by too high of a dose) and will pass long before the therapeutic effects of the cannabis subside.
2. Death is not a potential side effect of (short- or long-term) cannabis use.

As a provider, both of these are highly important points to consider. Cannabis in this regard alone immediately showcases a better safety profile than *every* pharmaceutical medication in our arsenal.

COMPARATIVE SAFETY PROFILES

In order to better understand the safety profile of cannabis, it must be compared to other substances. The following is a collection of pharmacokinetic safety profiles of various substances intended to demonstrate the effective comparison between other commonly used drugs and cannabis.

Caffeine

Most healthcare providers are not surprised to learn that caffeine is actually the most commonly used psychoactive substance in the world (Temple et al. 2017). Although caffeine is a low-risk substance, there are still potentially harmful associated health risks. Certain populations may be especially susceptible to potential vascular or cardiac-related problems (Temple et al. 2017). While the risk for caffeine as a cause for death is

limited, there have been occasions of caffeine-related tachyarrhythmia resulting in death.

Acetaminophen

For several decades, acetaminophen has been one of the most popularly recommended medications (Yue et al. 2018). Acetaminophen is a very safe medication that is available over-the-counter; however, any medication that contains this substance must include a warning concerning hepatotoxicity. Research suggests that acetaminophen overdose is fairly common among a large demographic (Wolf et al. 2012).

Acetaminophen is also difficult to detect in patients who have damaged livers and could be a contributor to liver failure (Leventhal et al. 2019). In most patient populations, acetaminophen at recommended levels is perfectly safe, yet a large portion of people regularly ingesting more than recommended doses of this medication which can develop serious and potentially fatal complications (Lexicomp, 2019).

Percocet

A combination of acetaminophen and oxycodone, Percocet is commonly prescribed for post-operative pain. Obviously, Percocet has the same associated risks as over-the-counter acetaminophen, as well as the additional risks that are associated with oxycodone such as constipation, shortness of breath, and coma, among others. Serious and potentially fatal side effects can occur when Percocet is combined with other drugs, and according to the FDA, this drug can be habit-forming. There are serious and potentially fatal risks associated with Percocet and other opium-derived medications.

Sertraline (Zoloft)

Sertraline is commonly prescribed for patients suffering from depression, OCD, and other anxiety disorders. It is much safer than most other antidepressants and can even be prescribed to pregnant and breastfeeding patients. That being said, Sertraline is highly plasma protein-bound and may interact with other plasma protein-bound drugs. Otherwise, it does not have a high drug to drug interaction profile.

Sertraline can cause gastrointestinal distress, sexual dysfunction, or headaches. This drug can sometimes have more serious side effects such as arrhythmia, hallucinations, seizures, shortness of breath, or in rare cases can cause death.

GENERAL DOSING GUIDELINES

The dosing of cannabis, as can be seen from all the factors leading up to this point, is initially a very complex process that becomes easier with practice. If cannabis were a traditional pharmaceutical like Marinol (a synthetic, isolated version of THC), where there is only one active compound, dosing would be simple. However, with the addition of all of the cannabinoid-terpenoid complexities and related entourage effects, dosing becomes more multifaceted.

The dosage range for synthetic cannabinoids is from 2.5 mg up to 20 mg, and can even be higher for chronic health issues and long-term cannabis users (Lexicomp, 2019). This dosage range is based on naivety to cannabinoids, therapeutic level, and the chronicity of the patient's disease process, as well as the individual patient's needs and tolerance.

The psychoactive effects of the cannabis plant begin for most patients at around 5 mg, with the average medical dose ranging between 5—10 mg (Sulak, 2018; Goldstein, 2016). That said, several studies have noted that the therapeutic effects of cannabis are first noticed with "microdoses," or doses that range from 1—5 mg. The problem is that there is not a "scientifically accurate" dose of cannabis for everyone due to the individual differences in ECS as well as the changes that occur to the endocannabinoid system in times of disease (Russo, 2011).

As with medications affecting mental health, starting at the lowest possible effective dose and then waiting for the medication to reach a steady state in the blood is the safest way to initiate cannabis therapy. Some patients will not experience a therapeutic effect or notice any effect at all during their first usage. The important point to remind patients of is that this is just like any other medication and it must be taken at regular intervals to be effective.

Off-Label Prescribing

An interesting comparison of how cannabis works is that of the use of propranolol compared with cannabis for performance anxiety. Using propranolol to treat performance anxiety is referred to as an "off-label use", meaning that the purpose of the medication being prescribed is not the originally intended use. This can occur for many reasons, including the condition being treated not having a currently accepted treatment or that all currently accepted treatments have been attempted (The Food and Drug Administration [FDA], 2018).

In this case, cannabis is much like a medication being used off-label. There are many disease states and symptoms that cannabis can be used to treat that are not currently accepted as being beneficial for cannabis use. This does not mean that it is not efficacious, but rather that the current research has not caught up to the patient-reported benefit. A fascinating aspect of this comparison comes when we look at the side effects. Cannabis and Propranolol share some common side effects including dizziness, drowsiness, confusion, and lethargy (Lexicomp, 2019), but that is where the difference in side effect profiles end. Propranolol has much more serious side effects including cardiogenic shock, syncope, liver dysfunction, heart block, and Stevens-Johnson syndrome (Lexicomp, 2019)

When it comes to harm reduction, side effect profiling is paramount to safely and effectively prescribe a medication. This profiling happens continuously when comparing the safety profile of cannabis to medications that are considered to be “safe” or “benign” by providers; the safety profile of cannabis is shown to be more innocuous than that of pharmaceuticals. As this is the case, when comparing most medications with the consideration of harm reduction, the safety profile of cannabis outshines all the rest. Cannabis can improve harm reduction for many patients by helping to decrease polypharmacy, especially in the elderly population (Alsuwaidan et al., 2019).

VARIABILITY IN DOSING

One of the most vilified aspects of cannabis therapy for many providers is the variability of effect that cannabis can have. This transience, however, is actually one of the most important therapeutic activities of cannabis. The variability of effect is part of the adaptability and homeostatic relationship that cannabis therapy brings to the table. This is what explains the “extra” effects that patients receive when they are using cannabis for one symptom (say, nausea for cancer) only to then receive the added benefit of cannabis’s analgesia. When used as a medication, the ECS tends to use the cannabinoids much the same as vitamin supplementation. This replacement has the intended effects in the target system, but the largest benefit of supplementation to the body is that all body systems begin to run much more efficiently. This synergy is similar to the way that cannabis therapy interacts with the body.

CONSISTENT DOSING

One of the more important aspects of dosing when it comes to cannabis is consistency. The importance of dosing and consistency in cannabis therapy has been known since the early 1900s, when Sir William Hale-White discussed specific dosing in his *Text-book of Pharmacology and Therapeutics*. It has already been noted that, like other medications, scheduled daily use is important to reach a therapeutic level. The other part of consistency with dosing is using the same amount every time, similar to the milligram content of a pill. If using edibles or tinctures, this goal is a little easier to achieve as they are dosed in milligrams like many pharmaceuticals. As such, this may be a dosing method that many practitioners are most comfortable with. It is much harder to accurately dose when it comes to combusted cannabis.

There are five factors that can change the dose a patient receives, and knowing about these factors can help mitigate the differences. These five factors are:

Dose or amount of medicine used. Accuracy in measurement is very important in the world of medication therapy. All pharmaceuticals we prescribe are dosed, most in milligram content, such as a Metoprolol 25 mg tablet. Most cannabis edibles and drops are dosed in the same way, making it simple for the patient to take the same amount each time. When it comes to combusted and inhaled forms, this consistency becomes slightly more difficult to achieve. If patients pack their medication every time they use (through the use of a joint or a pipe, for example), they should be encouraged to use the exact same amount each time they do so. This will help them with regularity in dosing. If the patient packs a whole bowl for multiple uses, it becomes more difficult to measure exactly how much a patient is using.

Area combusted. When a patient packs a full bowl for multiple uses, this practice becomes an important part of dosing. The size of the area that is lit by flame determines the concentration of the inhaled cannabis. For example, if a patient lights a small area of the bowl, the smoke will be much less concentrated than if they lit half the bowl. If the patient is unaware of how much of the bowl is actually lit, it can put them at risk for side effects due to potentially taking a larger dose than intended. Another point of note in this area is that the accessory used to consume cannabis will also affect the concentration of the medicine. For instance, a joint will

produce less concentrated smoke than a pipe, which in turn creates less concentrated smoke than a bubbler or a bong. Using these devices to consume cannabis will concentrate the smoke more or less depending on the type of device used, and this point should be taken into consideration when discussing dosing with patients. Which device and/or accessory a patient uses also goes hand in hand with the next factor: the size of the inhaled dose.

Size of breath. Also called the length of breath, the amount of time taken to inhale also impacts dose size, with longer breaths causing larger doses. Patients should be encouraged to take the same size of hit or dose every time so as to minimize potential side effects. As previously mentioned, most cannabis related side effects are dose related, meaning that they are related to taking too large of a dose. An interesting point of note for this factor is that many vape pens that use cannabis concentrate are designed to give specific doses for length of breath. For example, many pens will give a 5 mg dose of concentrate in a 3-second inhalation. Using a vape pen can help with consistency in dosing and can be an option many providers could feel more comfortable with due to the specificity and control of dosing.

Force of inhalation. This factor plays an enormous role in the dosing of combusted cannabis. The strength of inhalation is correlated to the concentration of the cannabis smoke. Working almost like a reverse bellows for a fire, breathing in forcefully will result in more of the cannabis medication to be burned and cause thicker smoke. Also, the force can cause the area of combusted cannabis to grow rapidly. Patients should be cautioned to take the same force and size of breath each inhalation. This practice can be encouraged by treating the process of medicating as an almost meditative time. The patient can take calming and deep breaths in preparation, which will help them find a rhythm to their breathing that they then employ for taking their medicated inhalation. Of note, most vaporizers are calibrated to stabilize the concentration of "the hit," making it difficult to accidentally breathe in harder than intended.

Holding breath. This is a "pro tip" that your patients may hear from their recreational-user friends. This old wives' tale states that if you hold your inhalation, you will enhance the "high" and thereby increase the medical effects of cannabis. This claim is not supported by existing scientific literature at all and this practice has been associated with barotrauma to the lungs. The effect that users feel may be related to the effect of simple

breath holding and the deprivation of oxygen to the brain rather than any enhancement of medicinal effects. Patients should also avoid this practice due to the potential for anoxic effects that may cause dizziness and falling.

GRADUATED DOSING

"Start slow, go slow" is often the advice given to patients at their dispensary, but it's a mainstay for medical practitioners as well, especially when special populations are involved. When trying to discover the optimal dosage for a patient, the best advice is to start with a low dose. From there, you and your patient can work together, slowly increasing the dosage to reach the optimal amount/dose for him or her. Again, the dosage level at which most patients begin to feel psychoactive effects is approximately 5 mg, and the dosage that is medically effective is between 2.5 mg and 20 mg.

As previously mentioned, some patients need only low doses of medical cannabis to achieve effective symptom relief. Cannabis has a multiphasic dose-response relationship. In high doses, it can have more adverse effects such as paranoia, anxiety, and a mitigation of beneficial effects for the patient. Since each patient's optimal dose varies, starting low is a wise course of action.

ADDICTION AND WITHDRAWAL

Another area of concern among many clinicians is the area of addiction and withdrawal. This is an area of caution with any medication; however, with cannabis the statistics are often skewed when considered through a medical lens. According to the National Institute on Drug Abuse (NIDA), around 4 million Americans met the criteria for diagnosis of cannabis addiction in 2015 (National Institute on Drug Abuse [NIDA], 2018). In contrast, some studies note that sugar (a benign food) addiction affects most of the obese population of the world (about 36.9%) (Westwater, Fletcher, & Ziauddeen, 2016). Both are somewhat frightening numbers, but when they are broken down against the criteria used to attain these statistics, things become less scary. When comparing sugar addiction numbers and the DSM-V criteria for diagnosis of substance abuse disorders, our patients would demonstrate addiction to many things including pharmaceutical medications when DSM-V criteria is applied:

1) Taking the substance in larger amounts or longer than recommended. Famotidine is the perfect example here. It is not recommended for long-term use, but many patients use it daily (Lexicomp, 2019)?

2) Wanting to cut down or stop using the substance but not managing to. This is a story every provider has heard. A patient dislikes a medication they are on and would like to get off but can't because they need the therapeutic effects.

3) Spending a lot of time getting, using, or recovering from use of the substance. This example cannot be applied to many other medications due to their legal status. However, consider that many medications come with the warning to avoid usage when driving because patients are unable to function normally. Patients spend a fair amount of time recovering the cognitive ability to carry out daily tasks.

4) Cravings and urges to use the substance. This criterion can be said of almost any pharmaceutical that has been used to a therapeutic level. Any missed dose will cause a drop in therapeutic levels, causing the body to drop out of homeostasis and "crave" what it needs to bring it back into balance. When cannabis is viewed as medication, the same can be said of it.

5) Not managing to do what you should at work, home, or school because of substance use. Ironically, for most using cannabis as medication, the opposite is true. Many use cannabis to overcome, for example, their public anxiety, allowing them to actually go into public situations that they would otherwise avoid.

6) Continuing to use, even when it causes problems in a relationship. This is a problem for many American households, especially when one person views cannabis as medication and the other views it as a drug. Such conflicting views can lead to tension in the household and for the person receiving therapeutic benefit from cannabis to feel unsupported and like a "bad" person.

7) Giving up on important social, occupational, or recreational activities because of substance use. As previously stated, many patients who use cannabis as a form of therapy use it as an

adjunct to overcome anxiety and allow them to attend public events. However, there is a part of this population that is forced to make the choice between the therapeutic effects of cannabis and, say, having a desired career due to drug testing and cannabis's current status as a federally restricted substance. This kind of discord can have a devastating effect on the quality of life of many of our patients and is a point that should be considered. Outside this social stigma, many who benefit from the analgesic effect that cannabis provides are able to be more active than they would otherwise be. Compare this therapeutic action to alcohol or even prescription painkiller addiction and the differences become quite clear.

8) Using again and again, even when it puts you in danger. The legality of cannabis comes into play here as the illegal purchase of cannabis is the danger placed on this patient group. There has not been a surge in automobile crashes as some people expected there would be with the legalization of cannabis in states like Colorado or Oregon. Furthermore, studies show a drop in suicide rates with legalization (Anderson, Rees, & Sabia, 2012).

9) Continuing to use, even when you know you have a physical or psychological problem that could have been made worse by the substance. This issue is fairly easy to address when it comes to cannabis. Most patients who use cannabis gain therapeutic benefit and do not have physical or psychological problems. For those who do experience problems, as with weighing any medication therapy, type (in cannabis the strain), dosage, and risk versus benefit must be considered.

10) Needing more of the substance to get the effect you want (tolerance). Developing a tolerance is common among many of the pharmaceuticals that practitioners use. Patients often develop a tolerance or display reduced effect from the medication requiring an increase in dose. If a patient is receiving therapeutic benefit from cannabis, why should that therapy be different in this regard?

11) Developing withdrawal symptoms, which can be relieved by taking more of the substance. This concern can be said of many pharmaceuticals with therapeutic benefit. The

withdrawal symptoms of cannabis include irritability, anxiety, sleep difficulties, decreased appetite or weight loss, restlessness, depressed mood, headache, sweating, and gastrointestinal pain (Miller, Oberbarnscheidt, & Gold, 2017). Interestingly, most of the symptoms that are listed as withdrawal symptoms here are also symptoms that are helped through cannabis therapy, making the argument even stronger for ECS and homeostasis.

All this is not to say that there is no such thing as cannabis addiction. Rather, it is meant to illustrate the point that we need to examine the issue much more closely. Viewed in this light, it becomes apparent that the criteria used to show addiction needs to be re-examined. The number of patients who are addicted to cannabis appears to be nowhere near the 4 million declared by NIDA, but without a more thorough and responsible reassessment of the criteria, the actual number will remain a mystery.

A FINAL WORD ON DOSING

"Is there an easy rule to follow?"

Many physicians ask this question, but unfortunately, there's no "easy" chart or other go-to solution to help find a patient's optimal dosage. As we learn more about medical cannabis, it may become easier to predict what dosage a patient will need. For now, medical practitioners and patients must work together to determine optimal dosages, often through trial and error.

Using medical cannabis effectively can be challenging, but many patients will find an optimal dose that provides them with effective symptom management. Making use of the information found in this chapter will be extremely helpful in guiding both patient and practitioner to finding the best treatment options using cannabis.

Marijuana Dosing: Quick Reference

- The dosage range for synthetic cannabinoids is from 2.5 mg up to 20 mg, and can even be higher for chronic health issues, with psychoactive effects beginning for most patients around 5 mg

- While the average medical dose ranges from 5-10 mg, it's best to start at the lowest possible effective dose and then wait for the medication to reach a steady state in the blood
- The effects of each dose can be somewhat variable, which is what allows for cannabis therapy's valuable versatility
- “Start slow, go slow” *and* stay consistent. From there, you and your patient can work together, slowly increasing the dosage to reach the optimal amount/dose
- For other factors to consider regarding how the patient takes in their dosage, be sure to review the guidelines discussed on pages 92 and 93.

Chapter 10

SPECIAL GROUPS AND POPULATIONS

> "When faced with making a recommendation for a pediatric patient, the questions I ask myself are, should there be a reasonable expectation that cannabis will alleviate this child symptoms and improve their quality of life and does this benefit outweigh any possible risks of adverse effects that can be attributed to this treatment? If the answer these two questions is yes, then I make the recommendation."
>
> —FRYE, 2018, P.P. 98

When discussing medical cannabis, as with all pharmaceuticals, there are certain groups of people who require special consideration. With cannabis, the three special population groups most associated with the need for additional caution are children (from newborn through adolescence), pregnant women, and geriatrics. The discussion of these groups separately from the general population is due to the fact that each one is vulnerable in its own way. Each of these groups has an individual set of needs, and each patient's history and condition should be carefully addressed case-by-case in order to determine whether cannabis therapy will be safe. (In the following chapter, we will discuss usage by certain "high risk" disease-state users with cardiovascular, pulmonary, or psychiatric conditions.)

CHILDREN

Children are among the most controversial members of the special population group, as well as the members who have received the most benefit from cannabis therapy. The controversy surrounding children using cannabis operates on multiple levels, but the primary concern is vulnerability related to their still-developing bodies, brains, hormones, and metabolism. This is a very valid concern, but when approaching cannabis as a medication, this debate becomes a little easier to navigate. The only controversy really becomes one of risk versus benefit, the same as we would weigh for any other medication.

Despite the controversy, children have been mainstays of the medical cannabis movement because of its relatively harmless safety profile, as discussed in Chapter 9, but also because of the great results this group has seen from the use of non-psychoactive CBD oil to help treat diseases (James Huntsman et al., 2018).

It should be noted that all CBD oil contains THC unless it is an isolate. Synthetic isolates, as previously discussed, can cause side effects due to their uninhibited effects (Mintz, C. S., Nison, E., & Fabrizio, A. J. (2015). The overall THC content in CBD derived from industrial hemp cannot have a THC content of higher than 0.3% of the overall dry weight by law ("Industrial Hemp | National Institute of Food and Agriculture," n.d.).

Analyzing Risk Versus Benefit in Children

The risk versus benefit analysis for cannabis use as a medication for children should be done on a case-by-case basis. No two children are alike in presentation of disease state, genetics, endocannabinoid system or response, and as such each child should be examined individually for risk and benefit. When considering cannabinoid therapy for children, the risk versus benefit of treatment should also not just be weighed for the individual disease state, but also compared to any pharmaceutical medication that would normally be used to treat the condition in children.

This is an often-overlooked aspect of cannabinoid medicine—that cannabis tends to be dismissed as "unsafe" while we continue to give children pharmaceuticals that can kill them. If a safer, more benign treatment is available, shouldn't that treatment be considered first? Many providers dismiss cannabinoid therapy out of hand due to its questionable legal status and cultural perception, but when considered as an actual medication, cannabis becomes a much more viable option than many other

drugs for the safe treatment of children.

Dosing for Children and Young Adults

This special population group requires tremendous caution in dosing. While the phrase "start low and go slow" is often used in the medical cannabis community to discuss dosage instruction with new users, it does not represent the high level of caution providers should use while graduating doses for children and young adults. Providers should start with the lowest possible dose (approximately 1.0—2.5 mg) and titrate very slowly for effect. There is no "one size fits all" cannabis dosing and every patient's individual cannabinoid need will be different. Be sure to keep this in mind and educate the patient and their parents; inform them that they may not see immediate effects and may, in fact, have to build up to a more appropriate therapeutic dose.

The final consideration with this special population is storage. Many children who use cannabinoid therapy dose with edibles. As with vitamins or other medications that may taste good, parents should use care to store their children's cannabis medications out of reach.

PREGNANT AND BREASTFEEDING WOMEN

Another controversial group, pregnant and breastfeeding women, is very important to discuss as it involves not one but two patients. The mother and baby should be approached as one unit, as any substance the mother consumes will eventually find its way to the baby (Paramore & Paramore, 2017).

There are several reasons that the discussion of cannabinoid therapy is important with this population: 1) the mother passes 2AG (an endocannabinoid important in immune function) through the breast milk; 2) cannabinoids cross the blood brain barrier; and 3) cannabinoids can actually *increase* the permeability of the blood brain barrier, allowing compounds that would not normally be able to cross to freely pass (Paramore & Paramore, 2017). These facts make this one of the most challenging special population groups to approach with cannabinoid therapy. Add to this the copious amounts of journal articles that condemn cannabis usage in this group, and it almost feels like they should not be approached with this medication at all.

Interestingly, when examined, most of the studies condemning cannabis usage in this population have one commonly occurring flaw: the

confounding inclusion of women who smoke tobacco (known to be carcinogenic and teratogenic) and other illegal drugs (opioids, methamphetamines, etc.). This occurs so often that it has made the American Academy of Pediatrics take notice, publishing a report in 2018 noting that whereas many other drug users miss prenatal visits, cannabis users do not (Ryan, 2018). The majority of the women who use cannabis during pregnancy are doing so to help alleviate symptoms like nausea or vomiting (Ryan, 2018).

It should also be noted that not a single state that has legal cannabis laws (whether medical or recreational) has a law listing pregnancy as a contraindication to either the recommendation of use or the dispensing of cannabis (Ryan, 2018) which is fascinating to note compared to many pharmaceuticals (pregnancy category X), or alcohol and tobacco (as cannabis is so often compared to).

This is not to say that cannabis usage in pregnancy is without risk. Studies have linked cannabis use in pregnancy to low birth weight and measures, pre-term birth, and anemia in the mother. It should be noted, however, that there were *no* relationships between cannabis and any of the other measures being observed; the American Academy of Pediatrics also noted that there is no control for the confounding variable that cigarettes and other drugs present (Ryan, 2018). This means that many of the adverse effects found by these studies that are attributed to prenatal cannabis usage could actually be caused by substances (tobacco and other drugs), substances *known* to cause these side effects. This flaw in research points out the desperate need for more reliable and valid study, especially in the case of pregnant and breastfeeding mothers.

GERIATRICS

The largest part of evaluating geriatric use comes down to safety. The psychoactive effects of cannabis have the potential to cause problems in the geriatric population, and when combined with the increased cellular permeability caused by both phytocannabinoids and terpenoids, the risk exists to potentiate some effects of certain medications. Caution should be used when approaching this population if combining cannabis with psychiatric or sedating medications so as to avoid potentiation of effects.

Luckily, many of these medications can themselves be supplemented or replaced by cannabis. Medical cannabis usage among the elderly has also resulted in decreased usage of prescription pain medications (Peters,

2013) and has potential to help with the polypharmacy problem faced by this population. Polypharmacy is the concurrent use of multiple medications by a patient to treat usually co-existing conditions and which may result in adverse drug interactions. Cannabis can help reduce the number of medications taken by patients for chronic conditions, which can help reduce incidences of polypharmacy among the geriatric population. Because of this providers must be very aware of potential interactions with currently recommended medications when prescribing cannabis. These interactions include medications metabolized by CYP 450 system, as well as medications which cause sedation or drowsiness. Interactions with the CYP450 3A4 have predictable effects on CBD concentrations with inducers like rifampin decreasing concentrations and inhibitors such as ketaconzole increasing them. However, given CBD's safety and lack of psychoactive effect these are rarely applicable clinically. (CBD may also have an inhibitory effect on 2C8, 2C9, 2D6, and 2C19, leading to increased levels of antidepressants, antiepileptics, proton pump inhibitors, clopidogrel, propranolol, carisoprodol, cyclophosphamide, Rosiglitazone, burprenorphine, montelukast, celecoxib, sulfonylureas, losartan, naproxen, phenobarbital, phenytoin, rosuvastatin, valsartan, and warfarin.) Until the patient knows how they feel on the medication, they should use the same level of caution as with any other prescription.

Outside of this caution, cannabis can be very beneficial for the geriatric population for many reasons. The analgesic and anti-inflammatory effects alone are extremely advantageous for this population, and the anti-anxiety effects have shown much promise in the treatment of agitation in patients who have Alzheimer's disease or dementia.

PATIENTS WITH MENTAL ILLNESS

Patients with mental illnesses, specifically bipolar disorder and schizophrenia, have garnered a lot of negative attention when it comes to cannabis therapy. The early onset of psychosis correlating with cannabis use is present throughout medical literature,. However, none of these studies account for the confounding variables of alcohol or tobacco, an enormous oversight that is vilifying a potentially beneficial treatment for this group.

The majority of studies that paint cannabis usage in mental health patients in a negative light fail to take into account the "chicken and egg scenario" when it comes to patients with bipolar or schizophrenia. One

study has shown the bias in approach to treating these disease states by pointing out that many patients who suffer from both disease states had never used cannabis before their diagnosis, and that these patients sought out cannabis therapy on their own as a way to self-treat their symptoms. Contrary to popular belief, there is actually very little data that associates structural changes in the brain with cannabis use. A recent study in *Neuropharmacology Today* notes that there is only limited data associating neurological structure changes with cannabis usage in young people aged between 14 and 22 years old (Scott et al., 2019). This is very different from what we are taught in most medical textbooks and literature but illustrates the difference between advancing through progress or maintaining the status quo through tradition.

The management of symptoms for these types of diseases can benefit from the usage of cannabis as an adjunct to traditional medical management and may actually provide protection against acute metabolic syndrome in psychosis (Vasquez-Bourgon et al., 2019). The largest caution with this population is that more moderate doses of THC should be used rather than high THC strains. This is due to the modulating effects of CBD controlling THC, so as to avoid the psychoactive effects. In fact, therapies using cannabis with high concentrations of CBD have been shown to potentially normalize dysfunction during episodes of psychosis (Bhattacharyya et al., 2018). Another important point is that, as with all other populations and cannabis therapy, these patients should be educated in using cannabis as a medication rather than an intoxicant.

Due to this change in thought process from traditional use, controlled, smaller doses should be used for effect, as large doses with high THC content have more potential for psychoactive side effects and the triggering of overall psychosis. More research is obviously needed into cannabis therapy in this population; however, the benefits are also apparent. Caution should be used when beginning cannabinoid therapy, and patients should start out using the lowest effective dose.

PETS

Pets are an often-overlooked population when it comes to cannabis safety. Most pets, like humans, fall into the vertebrate category and as such have endocannabinoid systems (McCamman, 2017). This means that they can enjoy therapeutic effects from cannabinoids; but it also means that human dosing does not transfer directly due to their small size and different

metabolism. This difference can cause potential for adverse effects. If cannabinoid therapy is being considered, a veterinarian should be consulted for proper dosing for the species of pet and for its specific weight. As with children, cannabis medication should be properly and safely stored out of reach.

The idea of approaching cannabis as medicine for special populations can be scary for many providers. However, when engaged with as a medication and the risks versus the benefits are weighed, cannabis becomes a much less intimidating endeavor. As providers, we must approach any patient, even one from a special population, with a holistic approach, taking into account the patient as a whole and weighing all available medication options to find the best for each individual patient.

Chapter 11

INDIVIDUAL AND GROUPED DISEASE STATES

> "Chronic illnesses that prompt a patient to seek out medical cannabis treatment have very similar basic symptoms...all of which are treated with cannabis. Although most conditions are not cured with cannabis, managing and sometimes eliminating these symptoms with a non-toxic natural medicine allows patients to experience an improved quality of life that is not controlled by illness."
>
> —GOLDSTEIN, 2016

As cannabis becomes popular among a growing number of people, patient and provider alike, a large number of patients have become curious about how to incorporate cannabis therapy into their healthcare regiment, and how it might affect their existing conditions. As more reliable studies are released proving the effectiveness of cannabis for a variety of ailments, providers are in a better position than ever before to develop an understanding of how cannabis and its therapeutic applications can affect each disease state or condition.

Cannabis therapy can vary widely depending on each individual's disease or condition from strain to application. The level of research for the various therapeutic aspects of cannabis is still severely lacking; however, the practical and clinical uses are being continuously documented.

The generalized health benefits of cannabis for these disease states include (Russo, 2018):

- Agitation: THC, CBD, linalool
- Anxiety: CBD, THC (low dose), linalool
- Psychosis: CBD
- Insomnia/restlessness: THC, linalool
- Anorexia: THC
- Aggression: THC, CBD, linalool
- Depression: THC, limonene, CBD
- Pain: THC, CBD
- Memory: alpha-pinene + THC
- Neuroprotection: CBD, THC
- Reduced Aβ plaque formation: THC, CBD, THCA

PAIN MANAGEMENT

One of the most effective areas of cannabis therapy is that of pain management. The CDC estimated that in 2016, more than 50 million adults in the United States suffered from chronic pain (Dahlehamer et al., 2018). Meanwhile, the Department of Health and Human Services considers the current opioid crisis to be a health emergency impacting tens of millions of people in the U.S. alone (Assistant Secretary of Public Affairs (ASPA), 2017). Given these statistics, providers *need* alternative ways to treat and manage pain. Thankfully, chronic pain is a qualifying condition for a medical cannabis card in most of those states that have medical programs.

A recent study in *The Journal of Pain* is the first of its kind to put subjective numbers on the relief that cannabis provides to headache and migraine sufferers. The researchers tracked almost 20,000 sessions where cannabis was used to treat headache or migraine. The study showed a decrease in the severity of both headaches (89.9%) and migraines (88.1%) (Cuttler, Spradlin, Cleveland, & Craft, 2019).

Another intriguing aspect of cannabis use for the treatment of chronic pain is that when cannabis therapy is combined with opioids to treat pain,

the amount of opioid needed to treat is substantially reduced. Opioid overdose death rates in states that have enabled medical cannabis access are about 24% lower than states that have not enacted similar laws (Bachhuber, Saloner, Cunningham, & Barry, 2014). This effect is so substantial in fact that the authors of a recent systematic review go as far as to state that:

"In contrast to the proposition that cannabis may serve as a gateway is an emerging stream of research which suggests that cannabis may serve as an "exit drug", with the potential to facilitate reductions in the use of other substances. According to this perspective, cannabis serves a harm-reducing role by substituting for potentially more dangerous substances such as alcohol and opiates." (Walsh et al., 2016, p. 21)

Cannabis exerts its effect on pain control through multiple actions. Blocking of inflammation is a major measure in pain control through the action of cannabis on COX-1, COX-2, and prostaglandins which causes a decrease in inflammation (Russo, 2011). Outside of this, there is a large expression of CB1 receptors in the midbrain, periaqueductal grey matter (PAG) and in the nociceptive input receiving substantia gelatinosa of the spinal cord (Manzanares, Julian, & Carrascosa, 2006). Cannabis also blocks the pain sensation through the activation of these receptors, similarly to the way opioids exert their effects.

GENERALIZED DEFICIENCY AND OVER-SUPPLEMENTATION

The human body is made up of multiple systems relying on each other as an aggregate, with something as small as a simple vitamin deficiency affecting numerous systems and causing symptoms varying in both location and severity.

Vitamin C is a perfect example of how a vitamin supplement taken for deficiency can affect homeostasis, creating ripples across multiple body systems. Symptoms of deficiency can include lethargy, dry hair and skin, dry eyes, bleeding gums, hair loss, pitting edema, anemia, and slowed wound healing; long-term effects can result in scurvy (Marieb & Hoehn, 2019). When a deficiency is alleviated with replacement, the symptoms are relieved as the body shifts toward a state of balance.

This is not to say that there is no possible adverse outcome to supplementation or replacement; providers must need understand that there can be too much of a good thing. Over-replacement of these deficiencies can cause toxicity; for example, symptoms of vitamin C in excess can include insomnia, diarrhea, nausea and vomiting (Mayo Clinic website, 2018) and kidney stones (Thomas, Elinder, Tiselius, Wolk, & Åkesson, 2013), among other issues.

Take a moment to consider what this means: that a substance the body needs to function appropriately, such as a vitamin, can have negative effects if taken in excess and this makes much more sense. In much the same way, cannabis' mechanism of action has a similar supplementation effect on the body through the endocannabinoid system, allowing it to have beneficial outcomes exerted on multiple body systems simultaneously. Likewise, as with vitamin supplementation, too high of a dose can cause unwanted or adverse effects. Neither vitamins nor cannabis are a panacea, but the similarity in the ability of both to affect multiple body systems and relieve numerous symptoms is imperative to note.

NEUROLOGICAL CONDITIONS

Cannabis is an effective therapy for many neurological and neurodegenerative conditions. Some of the conditions on which cannabis has been shown to have therapeutic effects include: pain (acute, chronic, and neuropathic), insomnia, seizures, stroke, meningitis, and Lyme disease (National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, & Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda, 2017).

Psychiatric conditions that cannabis therapy can benefit includes: depression, anxiety, panic attacks, PTSD, and OCD (Bearman & Pettinato, 2018; Ross, 2018). Cannabis has also shown benefits in treating addiction, with cannabinoid therapy helping reduce opioid and alcohol use (Bearman, 2018; Blesching, 2015).

There are also two controversial disease states that, while they have shown benefit from cannabis therapy, should be approached with great caution, namely bipolar disorder and schizophrenia (Goldstein, 2016; National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, & Committee on the Health Effects of Marijuana: An Evidence

Review and Research Agenda, 2017). Due to the complex nature of the psychological symptoms, cannabis therapy should not be initiated until symptoms of the illness are under control and no psychotic episodes are present.

NEURODEGENERATIVE DISEASES

Several studies conducted in the last two decades concluded that phytocannabinoids and other compounds found in cannabis are useful at slowing or possibly even reversing the effects of neurodegenerative disease (Russo, 2018) and possibly helping recovery from traumatic brain injuries (Kwiatkoski et al., 2012). Cannabinoids and terpenes may provide several useful therapeutic benefits that target symptoms in neurodegenerative disorders including the following: Guillain-Barre Syndrome, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, and traumatic brain injuries (Frye, 2018). Additional condition-specific information about neurological disorders will be explored below.

"In addition of being a potent anti-Inflammatory and antioxidant substance, cannabidiol can also inhibit anandamide uptake and enzymatic hydrolysis, and decrease inducible nitric oxide synthase (¡NOS) protein expression and nuclear factor (NF)-jB activation. The potential of cannabidiol to attenuate the excessive formation of peroxynitrites induced by glutamate could also contribute to its neuroprotective effects, as demonstrated by in vitro results pointing to its ability to prevent retinal apoptosis. Some of these effects have been associated with a reduction in intra-cellular [Ca2+]. Finally, cannabidiol increases brain adenosine levels by reducing adenosine reuptake, an effect that could also contribute to its neuroprotective effects." (Kwiatkoski et al., 2012)

Amyotrophic Lateral Sclerosis (ALS)

There is data showing that phytocannabinoids have neuroprotective properties, which may delay or possibly even reverse neurodegenerative disease (Giacoppo, Mandolino, Galuppo, Bramanti, & Mazzon, 2014). Direct cannabinoid therapy has been demonstrated to prolong the life of "ALS mice;" however, more significant clinical studies are needed to prove its efficacy further (Giacoppo, Mandolino, Galuppo, Bramanti, &

Mazzon, 2014).

Cannabis also helps by lessening many of ALS' associated symptoms such as pain, muscle spasms, insomnia, anxiety, and depression (Pellati et al. 2016). The therapeutic applications of cannabis can be complementary or serve as an alternative to other treatment options for the symptoms associated with ALS and can increase the patient's quality of life (Fernández-Ruiz et al., 2015).

Alzheimer's Disease

Cannabinoids are anti-inflammatory in nature and therefore help decrease neuroinflammation. Using CBD is an effective method of reducing inflammation, and CBD is full of rich antioxidants (Goldstein, 2016), with THC also blocking the production of enzymes that cause neurodegeneration (Lusk & Owen, 2017). Alzheimer's patients have shown improvement in symptomology using cannabinoid therapies, and THC has been a demonstrably better treatment than other pharmaceuticals in multiple studies (Lusk & Owen, 2017).

Multiple Sclerosis

The National Multiple Sclerosis Society states on its website that it "supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved" ("Marijuana FAQs," n.d.). Cannabis use in MS patients has been studied for several decades now with similar results, which indicate reduced muscle stiffness, reduced bladder disturbance, decreased spasms, and decreased neuropathic pain and sleep disorders (Mojaverrostami, 2018).

HEAD, EYES, EARS, NOSE AND THROAT (HEENT)

Conditions of the head, eyes, ears, nose, and throat have shown promise with treatment using cannabinoid therapy, with glaucoma being one of the first modern conditions that were recognized to benefit from cannabinoid therapy. Aside from glaucoma, cannabis has shown benefit in the treatment of skin conditions (Kupczyk et al. 2009), otitis media, otitis externa (Blesching, 2015), to function as a decongestant for patients who suffer from allergies and provides anti-inflammatory relief for diseases that affect the throat, such as strep throat (Russo, 2016).

RESPIRATORY

The benefits of cannabis to the respiratory system may surprise many practitioners; however, the terpene pinene is known to have bronchodilator effects (Bearman, 2018). This alone has shown promise in the treatment of asthma, COPD, and bronchitis (Blesching, 2016). More research is definitely needed into the effects of cannabinoid therapy in this system, but early results are very promising.

This is an area where the route of delivery is very important. It is not recommended that a pulmonary patient consume cannabis through combustion, for example. Vaporization is still controversial among some practitioners for this population as well; however, this delivery method is very similar to a nebulizer in the hospital or office setting. The cannabis is heated until the cannabinoids are turned into water vapor (a process starting at around 300°F) (Rahn, 2016). Since there is no combustion involved and only water vapor is inhaled, many proponents believe vaporization is a safer alternative to combustion consumption methods.

CARDIOVASCULAR

The cardiovascular system is another area of the body where cannabinoids have shown promise. Treatment with cannabinoids has potential in the treatment of hypertension, arteriosclerosis, and high cholesterol (Dabrowski & Skarjda, 2017) due to their blood pressure regulating and anti-inflammatory effects. This is another system that should be approached with caution in dosing method as the deleterious cardiovascular effects of inhaling combusted material is well-documented.

The reason for caution is that cannabis is metabolized by the CYP450 system (Lexicomp, 2019) which is responsible for the metabolization of many cardiovascular medications, as well as the potential to trigger cardiovascular side effects (anxiety, paranoia, and increased blood pressure) that cannabis can cause. Despite this challenge, vaporizing and other methods of delivery (i.e. tinctures, etc.) are preferable in the treatment of cardiovascular disorders. Current data is very exciting, but this is very much an understudied area of cannabinoid application, such that more research into this area is badly needed.

GASTROINTESTINAL

Treatment of disorders of the gastrointestinal system with cannabinoid therapy is becoming increasingly common. With irritable bowel syndrome being recently added to the list of diseases that make up endocannabinoid deficiency, cannabis is now a staple treatment of these disorders (Ross, 2018). Cannabis is also known to have antiemetic effects and is beneficial to those suffering from nausea and vomiting (Russo, 2018) from any etiology.

Gastrointestinal disorders known to benefit from the treatment of cannabis include anorexia, diarrhea, gastritis, irritable bowel syndrome (IBS), ulcerative colitis, Crohn's disease, and obesity (National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, & Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda, 2017).

GENITOURINARY/REPRODUCTIVE

Cannabinoid therapy has shown promise for the treatment of disorders of genitourinary and reproductive systems, especially when considering that there are CB2 receptors in both male and female sex organs (Ross, 2018). Disorders of the genitourinary and reproductive systems that benefit from cannabis are polycystic ovary syndrome (PCOS), premenstrual syndrome (PMS), pelvic inflammatory disease (PID), prostatitis, and urinary tract infections (Blesching, 2015; Ross, 2018).

ENDOCRINE

The area of endocrine dysfunction has shown tremendous treatment capacity when it comes to endocannabinoid therapy. Because of the endocannabinoid system's role in the hypothalamus-pituitary adrenal axis (Wyrofsky et al., 2019), cannabinoids have shown extraordinary potential in the treatment of hypo/hyperthyroidism, diabetes, and other diseases of endocrine dysfunction (Oláh, Szekanecz, & Bíró, 2017). This is a truly thrilling area of application for cannabinoid therapy, albeit one where more research is necessary.

MUSCULOSKELETAL

The analgesic and anti-inflammatory effects (Goldstein, 2016) that cannabis exerts on the body make it a viable treatment for musculoskeletal disorders. This is made even more evident when examined through the lens of cannabis' multiple dosing routes. Dysfunction can be treated through all dosing modalities to attack symptoms systematically. Disorders of the musculoskeletal system responsive to cannabinoid treatment include: sprains, strains, tendon injuries, ligament injuries, osteoarthritis, inflammatory joint disease, and fibromyalgia (Bearman, 2018).

INTEGUMENT

Cannabinoid therapy for integumentary disorders, though lesser explored, holds great potential for future treatment options. Topical application of cannabis in the form of an ointment, tincture, or lotion combined with a penetrating agent such as peppermint oil can give tremendous benefit for disorders of the integumentary system without any of the systemic side effects associated with ingestion (anxiety, psychoactivity, etc.). The anti-proliferative effects of cannabinoids can also help to control psoriasis (Kupczyk et al. 2009). Other disorders known to be helped with cannabinoid therapy include dermatitis, acne, generalized antifungal/bacterial/viral, eczema, and pityriasis (Goldstein, 2016).

DISEASES OF ENDOCANNABINOID DEFICIENCY

There is a growing realization among researchers and providers alike that, similar to every other body system, the endocannabinoid system (ECS) can have deficiencies and dysfunction. Diseases of endocannabinoid deficiency have emerged as a new area of grouped diseases that are based around dysfunction and insufficiency of the endocannabinoid system (Russo, 2016). Failure of the ECS to produce enough endocannabinoids (AEA and 2AG) to meet the body's homeostatic demands leads to a dysfunction that can present in several different disease states that now fall under this classification, including migraines (showing decreased levels of AEA), IBD, and fibromyalgia, Huntington's, Parkinson's, Alzheimer's, attention deficit disorders (ADD & ADHD) and autism spectrum disorder, all of which are currently being examined as potential diseases of clinical endocannabinoid deficiency (Goldstein, 2018; Russo, 2016). The majority

of these diseases have a common symptom, namely inadequate levels of Vitamin D.
Cannabis is known to help diseases of endocannabinoid deficiency through many different mechanisms of action, but could be even more impactful in the treatment of these diseases than is currently known.
Phytocannabinoids replace lacking endocannabinoids for people suffering from these ailments (Russo, 2016). One of the phytocannabinoids, CBD, contains large amounts of Vitamin D that help supplement the key deficiency, while the effects of the other phytocannabinoids treat many symptoms in various disease processes. The connection between endocannabinoid deficiency and Vitamin D deficiency is new but very promising (Guida et al., 2019). One interesting inference from this relationship is that diseases of endocannabinoid deficiency may be able to be diagnosed through testing of Vitamin D levels. This could provide faster diagnosis of diseases of exclusion, like fibromyalgia, and lead to better overall patient care.

Autoimmune and inflammatory Diseases

Cannabinoids have been shown to have significant anti-inflammatory effects through a variety of studies, as noted in previous chapters. Though much is yet to be discovered about specifically why certain phytocannabinoids seem to aid with inflammation, there may be a few reasons such as the induction of apoptosis, inhibition of cell proliferation, suppression of cytokine production, and induction of T-regulatory cells (Nagarkatti, Pandey, Rieder, Hegde, & Nagarkatti, 2009). Further study is needed into how the cannabinoid receptors CB1 and CB2 interact with phytocannabinoids in order to alleviate the symptoms of autoimmune diseases and other inflammatory conditions. However, this area seems to show significant potential for symptom reduction through cannabis therapy. Diseases that can benefit from treatment with cannabinoid therapy include Lupus Erythematosus, rheumatoid arthritis, scleroderma, Hepatitis C and liver disease, HIV/AIDS, and fibromyalgia (Bearman, 2018).

Fibromyalgia

While the symptoms of fibromyalgia are typically treated with a variety of medications including opiates, NSAIDs, muscle relaxers, antidepressants, antiepileptics, and sleep aids, cannabis can be used as a complementary or alternative therapy to these medications and for many of the symptoms experienced by patients who have been diagnosed with fibromyalgia (Goldstein, 2016).

Cancer

Cancer is one of the most widely accepted and frequently recommended conditions for cannabis usage. Most providers have at least heard of the anti-emetic and appetite enhancing effects of cannabis, but this is just the tip of the iceberg when it comes to the therapeutic applications of cannabinoids in the treatment of cancer. Many phytocannabinoids have been shown to have an apoptotic effect (Russo, 2016). This, combined with the anti-tumor and anti-proliferative benefits that many phytocannabinoids and terpenes (Goldstein, 2018) have been shown to have, makes cannabis a powerful adjunct for the treatment of cancer.

This is not to say that cannabis alone should be used as a cancer treatment; rather, cannabis should be used as a co-therapy with chemotherapy and radiation therapy for the treatment of cancer. Cannabis has been shown to have a synergistic relationship with these therapies, enhancing their effect (Goldstein, 2018).

Other often-overlooked benefits of cannabinoid therapy in this population are its psychoactive effects. The mood stabilizing and antianxiety benefits from cannabis can help these patients to cope with their diagnosis, treatment, and even with facing their own mortality (Bearman, 2018). An interesting aspect of cannabis therapy for the oncology patient is that many oncological providers recommend cannabis for their patients despite only half of these providers feeling that they had obtained enough cannabis education to do so (Braun et al., 2018). These providers have through their practice seen the benefit of cannabis to this population and determined it to be medically beneficial to their patients through reported effects.

FINAL THOUGHTS

Among the most important aspects of a provider's job is that of helping to alleviate their patients' suffering. Yet they need not do so alone—healthcare is no longer dictated by the practitioner, but is a joint team effort.

In view of this new paradigm, the continued disregard of cannabis as a treatment option, especially by reason of misinformation, can no longer be countenanced. The number of disease states that cannabis exerts a positive effect on is extensive and growing on an almost daily basis. The duty we as providers have to educate ourselves on available medications now includes the benefits of cannabis, which will allow for safe incorporation of more treatment modalities for the patient populations that we serve. The result of cannabis education will be improved outcomes and increased patient satisfaction, as well as decreased healthcare costs in general.

It is our task as providers to leverage our experience and ability to approach our patients non-judgmentally, in ways that will allow for open and honest communication, helping patient and practitioner to form a therapeutic partnership. Building this alliance will give provider and patient alike access to new treatment options with improved safety profiles over many pharmaceuticals, and lead to greater well-being for all involved.

GLOSSARY OF TERMINOLOGY

In any sphere of life, from sports to art, proper terminology is one of the keys to success. If a coach cannot communicate the game plan to his players in a way that they understand, there will be chaos. In much the same way, the success of the patient is dependent on the provider's ability to understand the vernacular that accompanies cannabis use.

The first part of terminology comes with the purchasing of cannabis from a dispensary. Many of the salespeople (or "budtenders" as they are known in the industry) are knowledgeable in many medical terms, but they usually talk about the use of medication in common slang. As such, it is important for a provider to acquaint themselves with these terms so that they can have knowledgeable conversations with their patients about cannabis.

WEIGHT TERMINOLOGY

These weight terms apply to the inhaled forms of cannabis, given in ascending order of increasing weight:

Gram: The base measure for cannabis.

Eighth: An eighth of an ounce, equal to 3.5 grams.

Quarter: A quarter of an ounce, which is equal to 7 grams.

Half-ounce or half: Equal to half an ounce. A half is 14 grams.

Ounce, zip, zone, or O: An ounce of medication, which is equal to 28 grams.

MEDICINE TERMINOLOGY

Bud, flower, herb, trees, ganja, green: The fruit of the cannabis plant and the part that is consumed. It comes in weights starting at one gram. This material gets packed into a vaporizer or bowl to be consumed through inhalation.

Joint, blunt, pinner, J, spliff: A rolled cigarette made of finely crushed or ground cannabis stuffed into a piece of rice- or hemp-based paper. It is consumed through combustion and inhalation. Usually such a cigarette comprises one to two doses.

Concentrate, wax, hash, crumble, pull and snap, rosin, shatter: Names for various types of cannabis concentrates (a mechanical process of isolating specific compounds). Usually the name denotes the consistency of the concentrate. Concentrates are usually consumed in vaporizing pens.

Edibles: Forms include candy (like chocolate bars and gummy bears), crackers, treats (like cookies and brownies), drinks (lemonades and soda), and others that are being newly developed to better suit consumer tastes and preferences. Not only do edibles come in various dosages, many edibles are formulated so that they can be broken up or otherwise divided for even more precise dosing.

Tincture: Usually glycerin-based (can be oil based) in a bottle clearly labeled that shows content of THC, CBD etc. per bottle and dropper...Tinctures are usually dosed in drops based on dosing needs.

Lotion, salve: Similar to other lotions and salves on the market in that they are applied directly to the area of need and exert their effects on site. This is an easy method for patients to control as there usually are no systemic effects.

Suppository: Cannabis can be made into a rectal or vaginal suppository that is usually dosed in a specific milligram content to give an exact dose per use.

Keif: The crystalline trichomes that can be seen on the flower or bud. Some keif falls off in the handling and grinding process. Many dispensaries will sell keif as a “bowl topper” or supplement for

medication. It is more concentrated in phytocannabinoids than the flower itself and, as such, should be used cautiously, especially by someone just starting to use cannabis.

ACCESSORY TERMINOLOGY

Lighter or fire: A key piece in almost every tool kit. Most users have a quality lighter even if it is disposable. It is a good idea to have more than one lighter, or a refillable one.

Grinder: A device used to grind cannabis flowers so that it burns more evenly and fits more easily into a joint or bowl. Typically, grinders are cylindrical with a rotating top that turns little interior metal spikes, or teeth, to tear up the flower buds. Many grinders have multiple chambers—one where the prepared bud will fall as it is crumbled by the teeth, and sometimes one below to catch the fine powder-like substance called kief.

Rolling tray: A tray that is used to roll joints and catch any loose cannabis during construction. It is usually made of metal and about the size of a paperback book.

Silicone mat: Used when handling concentrates, which can be sticky. Concentrates and tools used to interact with concentrates can be set on top of a silicone mat without fear of any material becoming attached to the mat.

Silicone concentrate container: Containers used to store concentrate. They are made of silicone like the mats to prevent the medication from sticking to it.

Concentrate or "dab" tool: Typically a metal or glass tool that is used to load concentrate into the device that it will be consumed from.

Scoop (or tongs): Many users prefer to use a tool to scoop the prepared bud into their bowl, but it is typically a small tool with a handle and end with a spoon or scoop, like a measuring cup. Though not necessary these small accessories can make the process of packing a bowl much easier.

Poker or "pokie" tool: The name is silly, but the premise is clear. It is a tool to poke with because when cannabis is burned it creates a residue that

is sticky when hot but will harden as it cools. Resin can clog up a piece so it is important to clean it often, using a pokey tool. These can be a pipe cleaner, small screwdriver, or similar sturdy metal rod.

Scraper or scrape tool: Scrape tools are similar to scoop tools in their function except they are more often used with waxes and dab rigs. Obviously, wax is incredibly sticky so when handling it you should not use your fingers. A scrape tool has a small flat, non-stick blade, like a putty knife, that can divide the wax and help load it into your vaporizer.

Rolling papers: These are papers, usually made of rice or hemp, that are used to roll cannabis cigarettes.

Crutch: A heavy paper used as a support in the end of a joint.

Rolling device or roller: This is a handheld device that is used to automatically roll cannabis cigarettes.

Pipe, piece, bong, bubbler, glass, rig: This is slang used to refer to a receptacle that cannabis is consumed from. It can be as small as a 3-inch glass pipe, up to a 20-inch bong that has multiple chambers for filtration to make a smoother inhalation. The piece that is best is a personal decision for each patient.

Ashtray: This is a small tray, usually about three inches in diameter that is used to dispose of the ash from smoking cannabis.

Storage or "stash" jar: Storage or stash jars are usually airtight containers that are used to store the cannabis medication.

USAGE TERMINOLOGY

Hit, rip, toke: These would all be terms that would be the equivalent to one inhaled dose of either vaporized or combusted cannabis.

Dose: Used most frequently by patients in reference to edibles, dose is one serving. This is usually used as in "my morning dose is a 10 mg piece of chocolate".

Drops: This is used when discussing tinctures. Patients start dosing with a

few drops depending on the concentration and begin increasing based on desired effects.

FREQUENTLY ASKED QUESTIONS

PROVIDER QUESTIONS

Why, as a provider, should I consider cannabis for my patient?
The recommendation of cannabis therapy to a patient, as with any other pharmacologic agent to be considered, is harm reduction. Which therapeutic route will have the smallest negative impact on the patient while having the desired beneficial effects? With the safety profile that cannabis has compared to most pharmaceuticals, cannabis should be a first therapeutic option for the treatment of many conditions.

What happens to my license if I discuss cannabis with my patient?
According to a 2002 federal court case, healthcare providers cannot have their license revoked solely for recommending cannabis. Outside of this case, the courts have regularly sided with providers regarding their need to be able to freely discuss anything, even illegal substances with their patients. The reason for this support is to give clinicians the ability to educate their patients with the goal of harm reduction.

What happens to my license if I prescribe a medical cannabis card for a patient?
Currently there is no "prescribing" involved. It is a recommendation to the local state cannabis regulating board stating that the patient would benefit from a medical card. The decision to issue such a card still resides with the individual states. Outside of this option, according to a 2002 federal court case, healthcare providers cannot have their license revoked solely for recommending cannabis.

How do i best talk about cannabis with my patients?
Open, honest, and non-judgmental conversations are best. Many patients are hesitant to discuss cannabis with their provider. Bringing it up in this

manner can help establish the patient-provider relationship and help build trust. The overall effect of this kind of communication will be that the patient has better overall health outcomes.

is cannabis a gateway drug to hard drugs?
This is a myth that was perpetuated by Reefer Madness and the War on Drugs in the 1980s. Cannabis is not a gateway drug; in fact, it has been referred to as an "exit drug" because of its ability to help patients wean off of much more addictive substances such as opioids.

is cannabis addictive?
Cannabis does not stimulate the reward section of the brain and, as such, it has fewer addictive properties than most medications. This is not to say that addiction is not possible, but rather that it is more rarely seen than in other addictive substance.

Can someone overdose on cannabis?
No, patients cannot overdose on cannabis. The amount of cannabis that would be required to be consumed by a single person in one dose to reach a lethal result is physically impossible to achieve.

Does cannabis cause lung cancer when smoked?
There are mixed reports in the literature regarding this topic. The majority of studies state that there is no correlation between cannabis smoking and cancer. To add to this discovery, many of the phytocannabinoids and terpenes in cannabis have shown to mitigate the effects of inhaled tar, which is associated with the development of lung cancer.

What are the side effects of cannabis?
The side effects of cannabis are short-term and seem to be dose dependent, meaning that they begin to occur at higher doses. Side effects of cannabis use include: a "high" feeling, increased heart rate, bloodshot and dry eyes, dilated pupils, increased appetite, impaired coordination and concentration, anxiety, paranoia, and potentially cannabis hyperemesis syndrome.

Are there different types of cannabis?
There are three different types of cannabis for the purpose of cannabis therapy: Sativa, Indica, and hybrid. Sativas are generally used during the day and provide an energetic and creative experience. Indicas are generally used in the evening and are associated with relaxation and sleep-aiding effects. Hybrids combine effects from the other two and can result in an

experience that “leans” in one direction or the other. For example, the strain Girl Scout Cookies is a Sativa-dominant hybrid, meaning that the Sativa effects would be more pronounced to the user.

is cannabis safe for special populations?
It is safe for most special populations. As with prescribing for any special population group, additional care should be taken, and the provider should weigh risk versus benefit for the particular patient in question.

Can cannabis be used with other medications?
Yes, it can. The only current caution found in scientific literature is that THC is metabolized by the CYP 450 system. As such, a patient should use caution when incorporating cannabis into her treatment at the same time as other medications that are metabolized by this system. Cannabis should be used one hour before, or two hours after, other medications that this system affects.

PATIENT QUESTIONS

Can I get arrested for having my medical card and medication?

The medical card is a safety net to help patients avoid harassment from authorities. As long as patients abide by the rules of the program, they should be protected. It should be noted that these rules vary from state to state and local laws should be checked. One of the largest variances between states laws are the products and concentrations of THC available and the amount of medicine that a patient can possess at one time.

What is the difference between cannabis and marijuana?
There is no difference outside nomenclature. Cannabis is the more proper term, being taxonomically correct. Marijuana is the term that was used to demonize cannabis and has roots in racism and greed.

What is the difference between CBD and THC?
CBD and THC are both phytocannabinoids. CBD is non-psychoactive and modulates the effects of THC. CBD also has many health benefits in its own right. THC is a psychoactive phytocannabinoid with many therapeutic benefits.

What are terpenes?

Terpenes are the essential oils found in plants that cause their smells. They have been shown to have numerous beneficial health effects.

How soon after I take cannabis will I see a difference in my disease symptoms?
Cannabis, as with any medication, takes time to build up to a therapeutic level. Some patients can have symptom relief for things such as acute pain after the first usage, but more chronic conditions may take more doses to achieve a therapeutic level.

Can I use cannabis with alcohol?
Cannabis increases the blood-brain barrier's permeability, which exacerbates the effects one can feel from alcohol. Using alcohol and cannabis together needs to be done with caution, just as with using alcohol and any other medication. This combination should not be attempted until patients know how cannabis affects them.

Can I use cannabis with opiates?
Cannabis has a synergistic effect with opiates, allowing them to work more effectively. This synergy can help those who take opiates to need fewer opiates over time. Cannabis can also help those wanting to wean off of opiates completely.

I have asthma; can I smoke cannabis?
Cannabis is a bronchodilator, so you can use cannabis if you have asthma.

I don't want to smoke; can I still use cannabis?
There are benefits specific to smoking cannabis, but there are multiple options:

- Vaping: inhalation of cannabis is very similar to a nebulizer treatment
- Edibles: food or drink that contains cannabis
- Tinctures: liquid form of cannabis that can be placed under the tongue.
- Capsules: contains liquid tincture
- Topicals: lotions or salves that you rub into your skin

I used marijuana in college, and i hated how it made me feel. Why should i consider cannabis now?

Usually those who have tried cannabis in the past did so just to get "messed up," and the quality of the cannabis was most likely low and/or the type of strain used was inappropriate for you. Taking cannabis as a medication is completely different, as you will find what dose and strain works best for you, possibly even using it daily like many other medications.

I have taken cannabis for a long time. is it dangerous to just stop taking it?
As with any medication, there may be symptoms of withdrawal that last temporarily. These can include symptoms that cannabis was being used to treat, i.e. insomnia, pain, anxiety, etc.

Why do people cough?
Patients cough when taking inhaled cannabis because the smoke or vapor that they inhale is an irritant. Cannabis can irritate the lungs, triggering the urge to cough so the body can purge the substance from its system.

I tried cannabis, and it made my anxiety worse.
This is a side effect that is usually related to the phenotype (Indica/Sativa), terpene profile, cannabinoid profile, and/or dose that was used. If you experienced adverse effects, one of these factors was inappropriate for what you needed.

I only use homeopathic remedies.
Cannabis is a naturally occurring plant, and if it is grown without pesticides, it is a completely natural remedy perfect for those who are looking for natural medications.

INTERVIEWS AND TESTIMONIALS

INTERVIEW #1

Interviewer: *How old are you, are you married, and what is your profession?*

Patient #1: I'm 36 years old, single, and I am employed as a manufacturing technician.

Interviewer: *What was your first experience with cannabis, when did you first hear about it?*

Patient #1: That is a tough question. I guess that I first heard about it in elementary school.

Interviewer: *That young?*

Patient #1: That young, yeah. I was actually getting into hip hop and rap. Gangster rap was taking off and Snoop Dogg was a big thing. Of course, Snoop is all about marijuana back in the day. Of course, my parents were very concerned about the drug usage [in the songs]. I didn't understand it, I just did kid stuff-hung out with my friends, played basketball, you know.

Interviewer: *So then, when was your first experience with the actual substance?*

Patient #1: My first experience was in college, actually. I got into college and met a couple of different people, artsy people. They basically were smoking while we were hanging out and sharing tips on art; I was really big into art at the time. They offered it to me, and I refused. When I really got into it was when I broke up with my fiancé at the time. I was going through a major problem, and literally my life wasn't going anywhere. I

was hanging out with some friends who were smoking (cannabis) and they said, 'Hey man, you want to smoke?' They didn't know that I didn't smoke at the time. I thought 'I've got nothing else to lose, my life is going to hell, so why not?' Yeah, it was a life-changing experience, I would say.

Interviewer: *How is that?*

Patient #1: Life-changing in that it made me...How can I say this...? I didn't know or understand chemically what it was doing for me at the time. All I knew was that it made me feel better and calmed down my anxiety.

Interviewer: *You found medical benefit, even though you didn't know that is what it was?*

Patient #1: Exactly.

Interviewer: *So then, what was your view on cannabis back then? I mean you obviously used it and realized that it wasn't horrible, but how did you view it—as a drug, a good or bad thing?*

Patient #1: I saw it as a recreational drug at the time. Smoke with my friends, kind of like drinking. A way to unwind at the end of the day. It went from minor use to almost constant use to the point where I actually stopped drinking for a while.

Interviewer: *Really?*

Patient #1: Yeah. I was receiving more benefit from smoking cannabis, I mean, you don't get hangovers from smoking (cannabis). What was even more interesting to me is that I was able to focus more on my college classes with the cannabis use. This time, I was in graduate school when I started smoking legit, and that was when I started learning more about it from friends of mine.

Interviewer: *That is really interesting. Have you ever been diagnosed with ADHD or anything like that?*

Patient #1: Actually, about three years back, I went through a bad break-up and nervous breakdown. My whole life I had been experiencing these problems. Long story short, I was diagnosed with PTSD. At the time I

didn't believe it because I was smoking cannabis, and due to this I wasn't experiencing symptoms. I actually had to quit cannabis for a probation thing, and I basically was not doing alright. I was always anxious, I was always paranoid, I was questioning my friend's motives, my anger was a problem. Things were getting worse, and after a year in therapy, I told my therapist that I wanted to try something to mitigate this. He wanted to try pharmaceuticals, and I told him I don't believe in them for these problems because my mother was on them for her mental health issues and they didn't help her. Addiction runs in my family. I asked him for a cannabis card. He signed it and here we are.

Interviewer: *So, you are currently using cannabis to treat your PTSD then?*

Patient #1: Yes.

Interviewer: *Did you try any other treatments for your PTSD before cannabis? You mentioned other medications, did they try antidepressants or sleep aids?*

Patient #1: He tried to push me on that at first, but as I said before, I explained why I did not want to do it. Those medications, my mother was on them and I had friends on them as well. They change who that person is. It doesn't necessarily fix the problem either; it might just fix one symptom. I have had friends turn to harder stuff like heroin because they couldn't get their medication.

Interviewer: *You are using (cannabis) for your PTSD. Have you found any other health benefits from your use?*

Patient #1: Yeah actually. I have sciatica in my back. I was involved in a bad car accident when I was 12 and my back hasn't been right since. There is always a constant pressure, not pain, more of an annoyance. What is funny is that the cannabis has helped to relieve it. It basically helps the pain to go away. It is refreshing, I am able to move more, exercise. It has been great.

Interviewer: *It sounds like you have had a lot of benefits from your cannabis use. Have you experienced any adverse effects? Using too much where you felt that you got "too high"?*

Patient #1: So, I have been smoking since I was about 20, so I have developed a tolerance to it over time. In the beginning it was a little rough because sometimes the highs were too intense. I didn't know how to come down, so I would try my best to alleviate the high. You know the old wives tale about sniffing coffee [to help you come down], I tried everything. But the more I learned about cannabis, its components, CBD, [the more] I realized that there is a lot more to this. I started getting recommendations from other people who deal with cannabis. I was able to find a solution to not get such intense highs.

Interviewer: *Have you discussed your cannabis use with your primary care physician?*

Patient #1: No, and mostly because I do not currently have one. But I have spoken to my optometrist about it and they are on the fence about it. They are not too sure about the effects, or they don't wish to speak about it.

Interviewer: *Did that make you feel comfortable talking to them or would that encourage you to talk to a primary care provider when you do get one? Or discourage you is the case maybe?*

Patient #1: It's a little bit of both honestly. One, as a patient I don't want to look like I know more about anything than my provider, I guess. Obviously online medical references have influenced a lot of people to feel like they can make their own diagnosis, so I'm very careful to try to not dominate a conversation in terms of medicine because I'm afraid that it's going to turn into a negative experience for me; discouraging use, trying other things, and the fear of negative propaganda that I've heard over the years.

Interviewer: *What I'm hearing is that you're afraid that they will look down on you because of what you know or what they perceive you to know, and you feel you can't necessarily be honest in that regard?*

Patient #1: Yes, but at the same time it's more of a legality thing, because at the time, when I wasn't educated about it as much as I should of been, I was still concerned about the legality of it even though it is medically legal in the state. It's still illegal on a federal level, and I didn't understand if I told my doctor and I'm doing something that he didn't prescribe is he going to report me to the cops or [he will] look at me like another drug

addict or some other negative stereotype and [I will] not be taken seriously.

Interviewer: *Do you feel like you've received proper education on your cannabis use? You sound like you've done a lot of research on your own.*

Patient #1: There was a time I hung around some growers. Knowledge was very limited that time, obviously back then there weren't doctors looking into it like there are now. There was research here and there, little tidbits, but nothing serious. It was mostly dealing with cancer. But as time progressed though, and people in the medical field started taking this more seriously, the knowledge expanded and I started picking up tidbits from medical students and friends in the medical field who took an interest in the subject. It really opened up my eyes to another world of what cannabis can do. It's just amazing because I was looking at the tip of the iceberg my whole life with cannabis. In the past four years I have learned more about cannabis than in the rest of my life.

Interviewer: *We discussed your comfort discussing this with providers, how do you feel about discussing it with family and friends?*

Patient #1: It was a hard subject with my parents. It's always been a touchy subject with them because they've heard all the wrong stuff ; it's just a drug or people use it to get high and have fun. Basically reefer madness. Over time, I hid smoking cannabis from them, but little did they know during this whole time I was able to tolerate my parents more. I didn't have a good childhood and my family and I didn't connect. This is mostly because my PTSD issues, but the minute I started smoking it they noticed the change. I was more calm and more myself when I was a younger kid. They noticed the change and the day I told them that I wanted to get my medical card they were very supportive of it. My mom took a stronger interest into it and she's been doing research here and there. They've been really supportive which is really weird considering they've been so anti-[cannabis] this whole time. It's honestly brought my family closer on a lot of subjects through talking about cannabis.

Interviewer: *Do you have any advice for new users or is there anything you wish you knew about cannabis use before he started using yourself?*

Patient #1: Don't be afraid to try it. You see everyone else using opiates and things like that. The side effects...change people. This is something

that can benefit people, give it a shot. What's the worst that can happen trying this?

Interviewer: *Have you ever had access difficulties? You said before that you were smoking and using it medically before you even realized it was medical. Before you got your medical card, did you ever have access difficulties getting your medication?*

Patient #1: In the beginning it was just a bunch of friends who knew a friend who knew a friend. Those were the hardest times because you're dealing with people you don't know that well and you really have to find someone you can trust. I've been involved in situations where it went really bad. But there [are] some people who are really good. It's a mixed bag when you don't have the legality behind it. It's scary. And at the same time you don't even know what you're getting [medication wise].

Interviewer: *To that, you said you been in some very scary situations. I'm sure this is a situation many patients have been in and providers don't really understand that. Would you say you are in danger physically? From the law?*

Patient #1: It's a mixed bag, because in the community everyone's really cool with everyone but there are some characters who are really shady. Some instances, for example the dealer I love will rob another dealer. You just happen to be hanging out with them at the time and it becomes a very tense situation. You don't know how you're going to react and it makes you think 'is it even worth it put your life on the line like this?' But at the same time, my mental health is important. What I'm doing and what I want to do with my life is important, but I need cannabis to be able to do that, so I feel stuck.

Interviewer: *So it's a choice between getting your medicine and being a functional human being?*

Patient #1: Pretty much. Yeah, be labeled as a criminal.

Interviewer: *That's a hard place to be in. Is there anything that you would say to a provider who is on the fence about prescribing cannabis to a patient?*

Patient #1: I would say definitely do the research. As a medical

professional, if you truly want to help people, I think it's your duty to help your patients and have the knowledge to provide safe treatment and better guidance in cannabis usage.

INTERVIEW #2

Interviewer: *Let's start with your occupation and age.*

Patient #2: Occupation insurance agent, age 84.

Interviewer: *You're still working at 84? That's impressive.*

Patient #2: Everybody says that.

Interviewer: *How many children and grandchildren do you have?*

Patient #2: I have five living children and I have eight grandchildren and seven or eight great grand.

Interviewer: *It should be noted that one of her daughters is here and she is in her fifties. When did you first hear about cannabis was it when you were a child, young adult, or a little bit later in life?*

Patient #2: Later in life.

Interviewer: *What was that like? Do you remember what your first thoughts were?*

Patient #2: I didn't think too much about it, but of course with a family member being in the business, I kept getting more and more. My son was telling me about how he had saved people because they were taking cannabis and I was pretty impressed with that.

Interviewer: *Did that change your perspective a little bit? Did you have a negative initial attitude towards cannabis?*

Patient #2: No, I really didn't. I just really didn't think much of it at all.

Interviewer: *What health condition are you using cannabis for?*

Patient #2: I have 7 nodules in my lungs and that's when I started on it. I

have been on it for about 6 months.

Interviewer: *Have you experienced any relief? Are you noticing any health benefits?*

Patient #2: I haven't, but they tell me my mind is better.

Patient's Daughter: She said she was more alert and we noticed that. She was more alert and she remembers things better.

Interviewer: *So you're having benefits that you didn't even expect when you started taking the cannabis?*

Patient #2: Right.

Interviewer: *You said your son was the first person to approach you about it, how did you feel when he first brought it up to you? Did that sound like a valid idea?*

Patient #2: I was up for it. The only problem is they haven't checked me for the nodules since I've been taking it, and I don't know what's going on in there.

Interviewer: *Have you experienced any bad effects from the cannabis?*

Patient #2: No, none whatsoever.

Interviewer: *Have you talked about Cannabis use to your primary doctor?*

Patient #2: No.

Interviewer: *Why not?*

Patient #2: I just didn't want to discuss it with her because she's so nonchalant about everything. She sits in front of her computer. She just does what she has to do and hardly checks me. 'Okay, you go get blood work done. Okay, you go to the rheumatologist, you go to the cardiologist.' She sends me all different directions and I don't get any help from her.

Interviewer: *Would you say it's the lack of trust?*

Patient #2: Yeah.

Interviewer: *Do you feel like you've received the proper education on how to use cannabis?*

Patient #2: I don't know what I could do different, or learn different, because I have these little bottles that I my put it in my coffee.

Interviewer: You drink it in your coffee every morning?

Patient #2: Yeah. I usually do it in the morning and at lunch.

Interviewer: *Are you taking the same amount every time?*

Patient #2: Pretty much.

Interviewer: *You said you didn't feel comfortable talking about your cannabis use with your doctor, do you feel comfortable talking about it with your family and friends?*

Patient #2: Oh, sure.

Interviewer: *Do you have any advice for new users or is there anything that you wish you had known before you started it?*

Patient #2: Well, I guess the only advice that I would have is that I wish they wouldn't be afraid to try it. My daughter has been taking CBD at night to help her sleep and it has been helping her. Because she's so uptight with the job and she needs something to help calm her down so she can sleep. I mean, I took it the other night when I wasn't sleeping good.

Interviewer: *So how did you sleep?*

Patient #2: Good! Not only that. Okay, to backtrack, I had a torn rotator cuff that was bothering me so I put rice packs on it, hot rice packs, and I go to bed with them and I still wake up. I will be hurting so bad, I would have to go microwave the bags again, you know. So I thought that was cool, you know rice is healing these things. I had sciatica on my right side and it was bothering me so I started with my gummies and I sat on a heating pad while I was watching TV and it seems to have helped it.

Interviewer: *So the gummies added into your treatment regimen?*

Patient #2: Yeah. Patient #2: I don't take them regularly.

Interviewer: *My next question is do you have your medical card?*

Patient #2: No.

Interviewer: *Is it that you just don't feel that you need that certification?*

Patient #2: Right.

Interviewer: *So you're getting benefit and you have supply, so there's not much reason for it?*

Patient #2: Yeah I just haven't gone that next step yet.

INTERVIEW #3

Interviewer: *We'll start with your age, occupation, are you married, and do you have any children?*

Patient #3: I'm 41 years old and am an oncology infusion nurse. I'm married with one child who is six years old.

Interviewer: *When did you first hear about cannabis?*

Patient #3: So, I grew up in the just say no or D.A.R.E to say no to keep kids off drugs era, so there was that. The first time I was ever exposed to marijuana was I think the first rock concert I went to. I was 11 and saw Don Henley with my parents. I smell this lovely smell (pauses, taking a deep inhale) and I said "Mom, what's that smell"? And she leans over, and says, and I quote, 'that's marijuana dear'.

Interviewer: *Was it a positive connotation? Negative, neutral?*

Patient #3: I feel like it was very neutral, and my mom did a good job of keeping it very neutral. Like told [me] that's what that smell was. Very neutral which was in keeping with the type of people my parents are. It was very interesting.

Interviewer: What about growing up and in your young adult life?

Patient #3: I had never seen anybody do drugs. I knew people who smoked, and I knew that was 'bad'. As a high-schooler... I was a nanny all summer, and a friend of mine was across the street for her nephew. Her aunt and uncle had some pot that she dipped into occasionally. It was one of those things like, 'okay, I'm not going to do that, but okay'. It wasn't a big deal to me. It wasn't like they were doing hard drugs like speed or heroin, you know?

Interviewer: *So, you're a current user now, what condition are you using cannabis for?*

Patient #3: I have chronic pain in my back and the main issue I have is migraines. I decided to get my cannabis card because I developed stage two chronic kidney disease from NSAID use, which is one of the less-common side effects of Advil. I don't have hypertension, I don't have diabetes. I don't have a family history of kidney disease, so I needed something to manage my pain.

Interviewer: *Who first approached you about using cannabis?*

Patient #3: Some very dear friends of mine.

Interviewer: *What were your thoughts at that time? You're a nurse, and this is something that has somewhat negative connotations in the medical field. What were your thoughts when it was brought up to you?*

Patient #3: I was more concerned about my job. I think that's why I didn't pursue it earlier. [For] issues with migraines I'd seen the neurologist and the medications...made my migraines worse. Some of them also have cardiac complications. The medical community didn't have a lot to offer me for my migraines outside of this and vitamin supplication so that began my search for something else. Through research I figured out the cannabis would actually work very well for me. That was a bit of a cognitive leap because I've never seen it used recreationally. I am however very grateful to have had the expertise and experience of my friends to nudge me in that direction.

Interviewer: *One of the biggest difficulties for you was the change between recreation and medicinal value. How long did it take you to first notice benefit? Did you notice with your first use, did it take longer?*

Patient #3: I noticed with my first use. And I'm assuming like many other cannabis users I noticed that it started helping with other things that I wasn't using it for, not just my chronic pain but my stress, my sleep, my anxiety.

Interviewer: *What other symptoms has there been benefit for?*

Patient #3: I have really bad PMS symptoms, and I'm perimenopausal right now, so I have very frequent periods that are more intense than usual and painful. The symptoms are getting worse. I have a vape pen at I was basically micro dosing myself other days I was not at work. My husband was the one that actually noticed and he said, "You didn't PMS at all this month". I had told him that it was because I was micro-dosing the whole time and that kinda blew his mind a little bit that I was using cannabis to achieve a certain effect, not to get "high". That kind of changed my mind and my husband's mind about it as well.

Interviewer: *So, you brought up your husband, does he support your use and does he use himself?*

Patient #3: He does. He doesn't like inhalation or smoking, and this is because his father died horribly from lung cancer and his parents smoked his entire childhood so he has negative connotations with smoking anything. However, he has definitely noticed benefits. He does not like the way marijuana smells, unlike me who at my first experience thought that it smelled magnificent. I think it's like the truly you either love it or hate it and he does not like it. But I have actually illegally shared my cannabis with him. He has trouble with insomnia and will wake up in a panic. He cannot get back to sleep. By dosing him with an Indica in capsules, because he 'can't taste the smells,' and he swallows them. Then, he's able to go back to sleep and stay asleep.

Interviewer: *Has he always been supportive or was he resistant?*

Patient #3: He was initially resistant, but I think his understanding and explaining to him that I gave myself kidney disease with Advil over-the-counter has made him more of a supporter.

Interviewer: *So, it was just the education that helped him to become a supporter?*

Patient #3: Yes, and seeing my personal experience and benefits.

Interviewer: *How long have you been using cannabis?*

Patient #3: This September will be two years ago, so little over a year and a half.

Interviewer: *Have you experienced any adverse effects?*

Patient #3: I have noticed with edibles that it is very easy to take too much. I started with these micro dose 5 mg THC chocolates when I first started dosing myself. I took just one of those little chocolates and I was playing Legos with my son and I realized, 'Wow, I am way too high right now.' I started to have a little bit of a panic attack and felt like I was dying but knew that I wasn't because the medical expertise that I have going along with this so I drink lots of water and went to lay down for a little bit...I have noticed that I can develop anxiety with too much.

Interviewer: *So, what you're saying is that dose control is very important?*

Patient #3: Exactly, and knowing what dose works for you, because that can vary wildly.

Interviewer: *This is an interesting question for you with your background in medicine and you being a licensed medical professional. Have you discussed your cannabis use with your primary care provider? And if not, why not?*

Patient #3: I have not. Because I am scared for my job. Even with HIPPA, my medical record is accessible by my job and I'm not comfortable taking the risk of having that information in my medical record.

Interviewer: *That is a valid concern.*

Patient #3: I did talk to my nephrologist before the last time I saw him. He said that [I was] the healthiest kidney patient he had so he didn't need to see me unless I had problems. He was asking of prior history of drugs that could've led to kidney disease. I mentioned that I had smoked pot a few times and he goes 'No, no, I'm talking about speed and hard stuff like that'. He said marijuana is not going to hurt your kidneys.

Interviewer: *Do you feel that you receive proper education on your cannabis usage?*

Patient #3: I feel like the research I have done and by talking to my friends I've been very well educated. But I feel that the education that I received going into a dispensary or in the act of getting my card was very lacking. I really felt like I was experimenting on myself.

Interviewer: *What advice you have for new users, or is there anything that you wish you had known before you started using?*

Patient #3: I think going over the benefits and drawbacks to smoking, vaping or oral ingestion would have been really beneficial. A brief overview would have been amazing. Then as far as smoking capabilities, I am totally intimidated by bongs, glassware, and very complicated smoking accessories. Aesthetically they are panic inducing and make me feel like I don't know how to use them. Education classes for new users would be very beneficial.

Interviewer: *Do you feel comfortable discussing your use with your family and friends?*

Patient #3: I do actually. I'm comfortable discussing it with my husband and my parents as well. My dad is that the opinion that marijuana is a gateway drug and that anyone who uses marijuana is going to start using opiates. He's basing this on personal experience of dealing with war veterans who switch from marijuana to heroin to help deal with their problems. The people who were self-medicating for PTSD. I've been trying to change his heart and mind about it. I am not so comfortable sharing the fact that I use cannabis with my six-year-old son, and that's mostly be felt because of the fact that it's still considered a schedule one substance by the federal government and I don't want somebody to call CPS because six-year-olds share everything with everyone at the most inappropriate times. I don't want him to stand in front of the class and go, "My mom uses cannabis". And then their parents go to the principal because they're concerned. That's something I don't want to have to deal with. That's really unfortunate though because it's medicine. I wish I could be upfront with him about it. It's easier to do when I'm filling the capsules in the evening for Jason and I to sleep because that's medicine, but trying to explain to a six-year-old that vaping or smoking is medicine, they don't quite understand that.

Interviewer: *Back to your nursing, what insight has your personal use given you into discussing this with your patients and helping your patients deal with their conditions?*

Patient #3: As an oncology infusion nurse, my patients are basically cancer patients dealing with side effects from cancer treatment which includes radiation, chemotherapy, and biotherapy. So I asked patients if they have their cannabis card and if they don't I strongly encourage them to get it. I let them know that if [they] need help, I can help [them] print out the paperwork that the doctor needs and I will advocate on their behalf to the providers. But then I also help educate my patients who have their cannabis card on how to use it appropriately and help them reduce their opiate usage, because they cause constipation, respiratory suppression, and frankly make patients pretty 'gomered' out. They reduce the quality of life. So if you use cannabis with your opiate pain medication, you reduce the need for large amounts of opioids and achieve greater analgesia. Being able to talk to patients about using concurrently is incredibly beneficial... I have also had Patients come back and tell me that that was very helpful information. They are no longer using as much of their opioid pain medication.

Interviewer: *On that note, is there anything that you've learned from these conversations that would give insight to a provider on how to approach a patient about cannabis?*

Patient #3: I found that by telling patients that it's not a panacea but is a very useful tool to have in your toolkit. Why wouldn't you try using something that could help your side effects? Results may vary; everyone is different. But referring to it as a tool to use is very helpful because it does have beneficial effects. I feel that most medical providers are aware of this. It's almost like a little bit of a joke — you have your card: you're trying to get high. But most providers I've talked to have said that this is incredibly helpful. I actually have a nurse practitioner with whom I was discussing cannabis in the oncology setting and she has seen that it has helped with their peripheral edema as well. She doesn't know how much of that is scientifically debased or anecdotal evidence, but she has noticed that it has helped patients with that and not just nodular pain relief. There are other things that medical cannabis can help these patients with. It's incredible.

Interviewer: *How do you feel that cannabis relates to harm reduction in medical patients?*

Patient #3: You know there's an opiate epidemic right now. Using cannabis in conjunction with opiate pain medications prevents the tolerance patients develop where you have to use more to achieve the same effect. Using cannabis in conjunction prevents that from happening. This is in addition to the other side effects that large doses of opiates cause. We joke about constipation, but that can be life-threatening. Having patients use less opioids so that they achieve greater analgesia and better pain control and have better cognitive function leads to a better quality of life. Cannabis in conjunction also reduces the opioids' side effects. So I feel like that is very important.

Interviewer: *What would you say to providers or patients who are on the fence about cannabis?*

Patient #3: I would let them know that it does have medical benefits. If you read the definition of a schedule one substance it clearly does not meet the criteria because it has proven medical benefits. Going back to that tool analogy, it is a very useful tool. Why would you not want to have as many tools as you can at your disposal to try and use?

INTERVIEW #4

Interviewer: *What is your age and occupation?*

Patient #4: 62 years old female, I am a midwife, and have four children, and four grandchildren.

Interviewer: *When did you first hear about marijuana and what was your first exposure to it? Were there any specific connotations involved with this exposure?*

Patient #4: High school. I had really good music friends that were into smoking. They were great friends who never made me feel uncomfortable for not using. They were very nonjudgmental.

Interviewer: *When was your first exposure to medical marijuana and when was the first time you ever personally had anything to do with?*

Patient #4: This year. I used too much and had a bad experience.

Interviewer: *What is the condition that you are currently using cannabis for?*

Patient #4: Chronic back pain. The first time I thought about it medically was in 2005. This was when [my son] was wounded in Iraq. He was going to need chemotherapy for his kidney condition and one of the sergeants at the base took me aside and explained that if he gets nauseous he should use marijuana and stated that he would help her. He said, 'I'll help you, but would you do it?' I said, "Absolutely." That was the first time I thought about it. I'm not going to have any qualms giving my son cannabis to help them through chemotherapy...we never ended up using any cannabis because his chemotherapy induced nausea was not that bad.

Interviewer: *Can I ask why you didn't use cannabis for him at that point?*

Patient #4: Because he didn't need it. He was managing the nausea fairly well on his own. If there was [a] need, I would've done it.

Interviewer: *Is your chronic back pain related to another injury?*

Patient #4: Yes, I broke my back...in a fall, and I have broken my back two other times in the past. C6, T4 and L4 were all broken. The pain was very intense. I didn't want to use opioids because they were not even touching my pain.

Interviewer: *Why did you decide to use cannabis this time as opposed to opioids and what opioids where you on?*

Patient #4: Initially, Percocet, two pills of 5/325 mg every 4 to 6 hours. And I was also on oral morphine as often as I could take it which is, I guess every six hours. I was also on a muscle relaxer Flexeril. It was all staggered but unless I was recently dosed with the morphine I was shaking with pain. The intense pain is what actually got them to do an MRI on me to find the break. They had not found the break initially and the intense pain caused them to look more closely and when they saw the break they said that [I needed] surgery [immediately]. Initially they wanted me to go home. After the surgery I was almost out a nonambulatory because of the pain. At some point before they set me on the switch me from Percocet to hydrocodone. I was taking two of those and they were 10 mg of hydrocodone and 500 mg of acetaminophen. When I saw my nurse practitioner seven days post-op and was going to get the refill of narcotics

she went ballistic. She looked at my chart and stated that I should not have had anything stronger than ibuprofen.

Interviewer: *For a broken back in your non-ambulatory seven days post-op?*

Patient #4: Even before that. She says we should have been using anti-inflammatories.

Interviewer: *Who did you first talk to you about medical cannabis then?*

Patient #4: Well, some good friends. It was a week or two before Christmas and they brought me a medicated chocolate bar. They handed it to me and I saw the cannabis leaf on the label. They said, 'You need to use this for your pain'.

Interviewer: *How did you feel about being approached about cannabis?*

Patient #4: I was relieved. Before that, my mother had raised me [in] counterculture. My mother said, 'Well you know Kathy there're cures for things like cancer. It's called cannabis. If I ever get cancer, I am using it.' My mother was a nurse and she was working in the system. She saw people get burned by the system because of lack of knowledge and openness to using other methods of treatment.

Interviewer: *So, you got the chocolate bar, the next question is when did you use it, how much did you use, what kind of effects did you get? Did you have any benefits the first time or did you need to take multiple uses?*

Patient #4: No, the first time I used it I was in pain. I was very confused on how to use the chocolate bar because the package said serving size 1 bar, servings per container 1.

Interviewer: *Did you eat the whole thing the first time?*

Patient #4: No, my friend had told me to 'go low and slow' with the dose.

Interviewer: *That doesn't tell you much, does it?*

Patient #4: No, it's like telling a driver that's from another country to get on the highway and just drive. There's nothing to gauge it off of. She had broken into pieces before I'd gotten it and I had a half of a square which

did nothing. Maybe three or four days later I had a full square which is 10 mg. Six hours later I realized that my pain was somewhat better and was able to fall asleep without back pain. It had been steering up until that point and keeping me awake. I didn't connect that it was related the cannabis. Especially because when I woke up I was still in less pain than I had been and didn't think that it was possible that it had that long of an effect. About a week later I had a migraine and the back pain together and I had been taking etc. and make migraine twice eight hours apart with no effect. The pain kept growing and the back pain was causing the migraine to worsen. At this point I'd gotten so nauseous from the pain I could barely walk, so I thought that one square did almost nothing and I took three squares. I do have a high drug tolerance. So my thought process was that three squares would not be too much if I've had anesthesia and woken up from it. So I took the three and 2 V hours later nothing it happened. My pain was still escalating. At that point I decided to take the remaining four squares that I had. 15 minutes later I was fine 20 minutes later I was fine.

Interviewer: *What exactly happened?*

Patient #4: Well, I was sitting on my couch and all of a sudden I was like I think it's just hit me. Then I realized that I wasn't shaking, but I thought all of a sudden that I was going to have a heart attack. All my senses were turned, up the TV was too bright, I had a candle burning and the smell bothered me. I put on my pulse ox in my heart rate was 122 and that my oxygen was 97%. I began to shaking with the fear of impending death I call the EMS. After they dispatched the ambulance I was talking the dispatcher and remembered that I had taken some cannabis. I told them this and the dispatcher relayed this to the EMS staff. They were phenomenal.

Interviewer: *So, the EMS staff was very well educated on what to do?*

Patient #4: So down to earth and so professional! I am so grateful. They came in and check me. I couldn't move from the couch. They checked my blood pressure and did an EKG and everything was totally normal. They started asking me questions and I could barely talk at this point because my mouth was so dry. They started to give me a little bit of water and then help me up a little bit. They walked me a little bit and helped calm me down. They said Kathy, we know what's wrong with you. You don't need to go to the hospital but will take you if you want. You're not having a cardiac emergency and you're not gonna die. It's the cannabis. I said no

way. They said yes, your paranoid. You've taken too much. They agreed that the labeling was very misleading. They were very understanding and said that they weren't even going to report the call so that it didn't go to my insurance. They offered to get me food and turn on music and reassured me. They said next time uses smaller dose. I said there won't be a next time. They said you're in a lot of pain and you're not now. It's helping you. They said this isn't uncommon but you will learn what works for you and how to use it. And if you don't, we'll come back if you need us. We'll even run another EKG if you need it to put your heart at ease, but your paranoia and thirst and all the symptoms are from taking too much cannabis. They were so knowledgeable and not rattled. I said why would people do this if this is how it makes people feel. They said because you have OD. You've taken too much and these are the side effects caused by that. It won't kill you. I then started laughing and they all laughed with me and we laughed and laughed; they refilled my water and then told me that the worst damage that was going to happen was that I would eat everything in the house. They told me to go to sleep, but I wound up doing some research and discovered that people who take too much feel like they're going to die. This was very common, and it reassured me. I face timed my daughter who is a cardiac critical care nurse and was hanging out with her friends. She looked at me and said that I looked fine. I passed the phone to the paramedics and they talked to my daughter. She laughed after she found out that I was fine. After the paramedics left, I decided I was just good to go down the line and talk to the rest of my children. I felt reassured and had quite a good time talking to them. I was able to sleep after that. I was talking to my son who was a (cannabis) user, and he said I don't know whether to be horrified or proud. He called me back several times over the next few hours to check on me. I was high for three days, but the worst of it ended in about 6 to 8 hours. The next day while I was still high, my daughter, who was a regular user said that if I wanted to come down to chew on some peppercorns. I said "I know I'm not dying and I'm fine now. I'm finally out of pain".

Interviewer: *Most people who have adverse effects as bad as you did swear off cannabis completely. Why was this not your response?*

Patient #4: Because [the EMS] told me that it was okay. They said that it was therapeutic. They told me that they would much rather have to come out for me having taken too much medical cannabis than too much hydrocodone.

Interviewer: *So, it was actually the EMS that told you that it was okay?*

Patient #4: Yes. They were very professional. And I talked to my primary care [provider] about it again.

Interviewer: *So you had talked to your primary care provider about your medical cannabis use?*

Patient #4: She was very supportive. She said, "I support that". She said I support you using medical cannabis. Do you have paperwork for me I will sign it here. I said I don't because I thought I had to fill it out online. I walked into one of the local dispensaries and they asked if I had a card. I said no but how do I get it that's why I'm here. It was hard for me to get out of the car and walk into the dispensary.

Interviewer: *Why was that?*

Patient #4: Because I was feeling a little [anxious]. I'm recognizable in town. What would people think? Then I thought, 'No, this is the responsible thing to do. I have no problems walking into a drugstore.' I drink the occasional glass of wine, but even that has bad connotations. My mother was the nurse in South Dakota in the 70s and 80s who actually talked about getting cannabis to her Patients. It was prescribed and she saw what amazing benefit these Patients received. I actually called her as I was coming down and told her what had happened and she laughed so hard.

Interviewer: *With any other psychoactive medication people are concerned and especially with medical cannabis.*

Patient #4: Well, exactly. People from my generation have a skewed perspective on medical cannabis because of the propaganda from the government and media. This has been demonized so much people are very cautious to even explore it. After the benefits that I have received from medical cannabis I knew I had to get my card.

Interviewer: *Do you feel that you have received proper education on your use?*

Patient #4: In the initial, no. 'Low and slow' means nothing. My son, who is a longtime user, was very knowledgeable. He took the time to educate me.

Interviewer: *Do you feel that you got the best and most useful information from the recreational user?*

Patient #4: I never thought about it that way, but yes, I did. He had his wisdom teeth out the week before and told me they had given him a prescription for Vicodin, which he never filled. He told me that he managed his pain completely with medicated gummy bears.

Interviewer: *Do you have a very strong support system and knowledge base now?*

Patient #4: Yes.

Interviewer: *Do you have any advice for new users or their new thing that you wish you would have known before you started using?*

Patient #4: I wish I had known what 'low and slow' [really] means. What are the activation times what is the earliest and latest that I might feel things. When you get your packet from the state, which took about a full four weeks. There's a little booklet of information where they suggest that you keep a journal of strains and symptoms and relief. I stopped at Walmart immediately and made my own journal. I have only used edibles and have had one other incident where I took too much.

Interviewer: *A vape pen might be a good option for you. Have you ever considered using one?*

Patient #4: That sounds perfect. I have a difficult time dosing with edibles because of how much it affects me. I can't do what I need to do in my daily life if I take an edible. I definitely don't trust myself to drive under the influence. I have been doing a lot of research on my own and have learned about the layering of methods to attack the pain at the same time. I have been taking a gummy every time I have pain and it's gotten to the point where it isn't working the same... I may be developing a tolerance.

Interviewer: *Tolerance is something that does happen. You have to vary your methods of consumption to avoid this. This includes changing up strains, how you use, and what you use.*

Patient #4: I don't have anybody on my healthcare team who doesn't know that I use, and not only that, I don't have anybody who isn't

supportive.

Interviewer: *You said that all your providers and care team know and are very supportive. How would it change things if one of your team was not supportive?*

Patient #4: I just wouldn't tell them.

Interviewer: *So, you would keep using without their knowledge?*

Patient #4: This works for me. If a provider can't understand that, they don't need to know that I use. I feel like everybody is very supportive of my use on my care team.

Interviewer: *So you feel empowered in your healthcare, like you have a partner?*

Patient #4: Yes. When the doctor imposes their plan on me instead of including me as a partner it's... Let's just say I'm not going to tell them off, but I'm not necessarily going to do what they say.

INTERVIEW #5

Interviewer: *Can you tell me your age, occupation, and marital status?*

Patient #5: I am 32. I am a stay-at-home dad and a blogger. I'm married to a nurse and have one child who is three years old.

Interviewer: *When did you first hear about marijuana in your life?*

Patient #5: I first heard about it probably when I was a kid. My mom thought she found a plant growing in the backyard and I saw her killing this plant. She was being mean, just killing this thing. She was like 'you know what that is?' And I said no? I was pretty young. She said 'That was a marijuana plant.' Now to this day I'm not sure that it was, it could've been a Holly tree for all I know. My mom is pretty good with plants, but I don't know. So... my first experience with marijuana was seeing my mom go crazy over a plant. She also told me stories about how mad my dad would get when my uncle would borrow his car and leave hemostats, which were used as roach clips [for holding the last little bit of a marijuana

cigarette] in his car. He would get really mad about those things.

Interviewer: *How did this shape your view on cannabis?*

Patient #5: Well, typically I was against any type of drug use whatsoever. I grew up in the Southern Baptist Church, and one of our covenants was never to drink ever... My mom made a deal with me that if I never drank [alcohol] or did any drugs, when I graduated from high school, she would pay for half of a new car for me.

Interviewer: *That's quite the motivator. You would say that your view on cannabis was negative then?*

Patient #5: Definitely. I was very much adamantly opposed to marijuana use when I was a teenager.

Interviewer: *So, then when did you first use?*

Patient #5: It was in my best friend's driveway when I was 21.

Interviewer: *What brought about that change from being so anti-drug to trying it? Because at this time it was still very illicit, correct?*

Patient #5: Correct, this is still Alabama. It was viewed very negatively, especially in Western Alabama. At the time, I was going through a lot of things in life. I was very depressed. I had all kinds of things going on; I was near suicidal, honestly. I spent a lot of time talking my best friend, just standing in his driveway. One night, I guess he was tired of waiting. I knew he smoked, but he never smoked in front of me, and he pulled out a little pipe I guess to see how I would react. I was smoking a cigar at the time. He took it out and he hit it, and I was like 'what's that?' He was like 'What you think it is?' I said it look[ed] like weed. He said that's exactly what it [was and asked if I'd like] to try. I was like 'Let me try it.' He looked at me and he was surprised because he knew I had always been very much against it. At that time I was very depressed and I just started drinking and smoking cigarettes to cope. To me I guess it was a time of my life where I was trying new things. I hit it, and it was godawful. At the time he didn't know much about it, he had just started himself. He put everything in there.

Interviewer: *By everything you mean?*

Patient #5: By everything, I mean the seeds, the stems, everything that came in the bag from the guy he got it from. He put it all in the bowl and smoked it. It cause [d] very rough thick smoke and [made] you cough really hard.

Interviewer: *What was it like?*

Patient #5: I didn't really notice much. Most people say don't really feel anything your first time, and I really didn't. I feel like part of that is the amount of caution that you use the first time smoking it. You hit it and you immediately blow out as though it's like a toxic poison. The next time you find out that, oh no, it's really not. I really think that the first time is a big part of it.

Interviewer: *You are a current cannabis user for medical conditions, correct?*

Patient #5: Yes, I am.

Interviewer: *What condition are you treating?*

Patient #5: I have an Endocannabinoid deficiency that has been typically diagnosed as ADD, anxiety, and depression.

Interviewer: *You use for all of those conditions?*

Patient #5: Yes, among the other benefits. Patient #5: I can say since I've started using medical cannabis, my overall profile of health has continued to improve. Before I began using cannabis I was overweight, I was on my way to high cholesterol, which I found out at the age of 27 ... and I had a lot of things going on with my mental health. All in all...I was going the wrong way and can say that there were tremendous medical benefits to using cannabis. These benefits are the point that...I don't use any pharmaceutical medications.

Interviewer: *Addressing those mental health benefits, what benefits would you say that you received?*

Patient #5: It's the best antidepressant I've ever taken, hands down.

Interviewer: *Why is that?*

Patient #5: I have experienced those thoughts of suicide, and those thoughts of dark places and not knowing what to do or the way out. I've been in places where you feel like you have no way of appreciating life whatsoever, I've been there. [I haven't had these problems] since I started using cannabis, other than a few times that I have been out...

Interviewer: *Out of your cannabis medication?*

Patient #5: Yeah, sometimes you can't find it. You call that being "dry".

Interviewer: *This would imply that you are not a medical card holder?*

Patient #5: I just recently moved to a medical state and have gotten my card. I have lived in Alabama most of my life and experienced a lot of the black market.

Interviewer: *Let's discuss that a little bit. Most providers have no experience with this. With the black market come its own risks and challenges. Have you ever felt like you were in danger in an attempt to acquire medicine?*

Patient #5: Oh there were lots of times. It's been less recently, but I've certainly been in parts of town I had no business being in, as residents there have told me. I have definitely gone into situations not knowing whether or not I'd have to deal with undercover law enforcement. There have been plenty of times where I have been worried about my safety and well-being. At the same time, it's worse to be suicidal and depressed. That's worse.

Interviewer: *So what you're saying is that you are putting yourself into a bad situation to prevent a worse situation?*

Patient #5: That's how I feel about it. That's how I felt about it since I started using and really realized that it is a medicine.

Interviewer: *What other benefits have you received from using cannabis?*

Patient #5: Throughout my adolescence and even up until now, I've experienced all sorts of gastrointestinal problems. I'm sure they related to stress, anxiety, and depression, but once I started using cannabis I realized I wasn't having those problems anymore. Also, in the last five years my

cholesterol has gone from elevated to normal. This is with no change in diet, exercise, or any medications other than cannabis. Not only that, I am at a healthy weight whereas I was obese before I started using cannabis.

Interviewer: *Let's go back to the black market for a minute. This is an area that prescribers don't have much experience with and are very nervous about. Have you noticed any difference in quality between what you find in the black market and what you would get from a medical dispensary? Also, I know that some physicians are worried about additives from the black market. Have you ever experienced any of that?*

Patient #5: I myself have not come across anything that I felt was adulterated. Every now and again you might find something that is closer to hemp and not really medical quality cannabis. We call that 'dirt. Honestly, it's night and day discussing the difference between the black market and a regulated cannabis market whether recreational or medical. If you go into a store and discuss a product with a Budtender or shop keeper who even doesn't know what they're talking about, they can at least give you the name of the strain and tell you where it came from. On the black market it's a guy that pulls up next to you in a car. You roll down your window, he rolls down his, he throws the bag of bud, and you toss over the money. This is how you buy your medicine.

Interviewer: *So, you don't know what you're getting?*

Patient #5: Absolutely not. If you know what you're getting, it's because the guy you got it from...got it from a legal state. Honestly, that's how it's been for a long time.

Interviewer: *With the recreational use, how you originally started, there's not as much emphasis on dosing. How would you say that that has affected your use and have you experienced any adverse effects from your use?*

Patient #5: It's almost like if every medication at Walgreens came without a label on it... So, you grab a box and either these pills work out for you, or they don't. If they don't, tough [expletive], they're the ones you bought so they're the ones you're using. That's how that works.

Interviewer: *It sounds like you've experienced some adverse effects?*

Patient #5: I can't say I've ever 'overdosed' on cannabis. I can say my

first time that I felt anything, which was the second time I used, I was introduced to all kinds of apparatus that were really designed to get you just [expletive] up. That was the intention.

Interviewer: *You are presented with the apparatus without very much information about how to use it and...?*

Patient #5: The guys that were helping me, [they were] my roommate and my best friend. When they set me up, they would explain.. how you hit it. By 'hit it' I mean how you smoke. They would explain the process, and then they would demonstrate, and I would try to do the same thing. Typically I could, however, the way they smoked, and the quality of Bud was so god-awful that typically you would try to inhale and, if you weren't experienced, would immediately blow out. If the device was filled with water, water was going everywhere. I can say that I was somewhat informed, but it's certainly a process if you don't know what you're doing. It's one of those things that you get better at with experience. *(It should be noted at this time that the Patient is medicating in the middle of the interview.)*

Interviewer: *Why did you feel the need to medicate right now? Is an anxiety thing?*

Patient #5: Typically, the reason I need to medicate throughout the day is so that I can maintain a steady normal feeling. What I find is that if I spread my doses out too far I will feel these ups and downs in mood and stress level. I like for it to be more of a steady-state.

Interviewer: *You've gone from recreational use to medical use. Have you discussed your cannabis use with your primary care physician?*

Patient #5: I do here because it is a legal state. I feel that it's important to be completely honest with my primary and every doctor, because studies are showing that when [cannabis is] not accounted for there can be complications. For me, I can say that [during] dental work, the numbing agent Novocain is not as effective on me.

Interviewer: *Do you feel you've received proper education on your cannabis use?*

Patient #5: At this point, I feel I've done most of the research myself. I've

discussed it with some of my close friends that I trust because they are healthcare professionals.

Interviewer: *Would you say that you have received any kind of cannabis education from medical providers outside your friend group?*

Patient #5: No, if you mention cannabis use in Alabama typically the doctor stops whatever he is doing, stares at your files, and says something to the effect of 'You shouldn't do that.' From there he probably never prescribes any type of controlled medication again. I typically don't take anything stronger for pain than ibuprofen 800 mg for intense pain, and that is extremely rare. I have taken Lortab before, but I don't like the way they make me feel they don't really kill pain, they make me itchy.

Interviewer: *You said that you're fine discussing this with your friends, what is your comfort level discussing your cannabis use with your family? How does your wife feel about it?*

Patient #5: My wife is an oncology nurse, so she is pretty well versed in it. I should say, rather, she's very sympathetic to its use with her patients. As far as my extended family goes, it depends on who it is. I have never talked to my grandmother or grandfather about it. I know they were children during the time of reefer madness, and they grew up with that attitude surrounding cannabis. Because of this I don't really feel comfortable talking to them about it. [As for] the rest of my family... if they are interested I will talk about it. My mother for example, her attitude has changed 180°. She was adamantly opposed to it when I was a child, as I said before, but now supports my use and some of her friends use because she understands that it's medical use now. I remember one time that I was visiting her, I had lived with her when I was very depressed and suicidal and she said that I had scared her during those times. She'd see me on prescription antidepressants and she didn't like it. After I moved away and came back to visit she asked what [I did]... I was like 'Well mom, I smoke a lot of weed now. That's about it.' She said 'Well I don't like it, but whatever you gotta do.'

Interviewer: *You alluded earlier to your illicit use and your 'dry periods'. You have had access difficulties. How has this affected you and have you done anything like put yourself in danger to get access to your medication?*

Patient #5: Well, not only that, but when I was younger [and ran] out, [I found] other substances to substitute with. Patient #5: When I was much younger, it was literally whatever I could get my hands on. One time I took an Ambien and then drove a car not knowing that Ambien would work so quickly. Luckily I got home. I have taken methadone before. I have taken all kinds of pills that I have had no business ever getting my hands on just trying to deal with whatever problems I was experiencing: stress, depression, and insomnia. Whatever problem happened to me at the time, I would find whatever I could if I couldn't hold of cannabis. To that end, when I got older it became drinking. My wife became a travel nurse and I had been a bartender, so I had plenty of access to alcohol in the Gulf Coast. We moved west, and the medical programs were not to the level where they are now. You had to have all kinds of documentation to prove that you had whatever condition and had tried other treatment options. At that point I made a decision that I was going to try to make a go without cannabis. I was going to try to manage all these things with alcohol. I threw away all my paraphernalia: scales, pipes, bongs, all of it. I packed it all and threw it in the dumpster. Then we moved across the country, and I found myself walking to the liquor store just to buy some booze. After my wife fell asleep I would walk to the grocery store. She knew I would be up late anyway because I was in school at the time and would be up late doing school work. When she was finally asleep I would walk to the grocery store and buy a six-pack or a four-pack of pints [beer] just so I could hopefully fall asleep. I was doing that for months.

Interviewer: *So, what you're saying is that lack of access caused you to substitute with a potentially more harmful substance?*

Patient #5: Yeah, absolutely. I was a lot less healthy when I drank that much. I made a conscious decision that cannabis was the thing. I had quit cigarettes when I was younger because they made me feel like that and I knew it. The same thing happened with alcohol and I knew I had to make that change. What made me realize it was the times that I did have cannabis I was fine. When I was out of bud, I'd wake up, go a few hours, and then start drinking.

Interviewer: *Do you have any advice for new users or is there anything you wish you had known before starting to use?*

Patient #5: I wish I had known that it was a medicine before I started. When I started I treated it like a college kid with a bottle of liquor. You

just keep taking shots and that's what you did until you felt okay. You kind of end up treating [cannabis] the same way. I wish I'd done more research also. If I was to advise a new user, most importantly I'd say give it a shot. Actually, try it twice. And for those who are hesitant about smoking it, vaporization and combustion are two completely different things. If I had to compare the two, I'd say vaporization is closer to a medical treatment. I've been doing doctors office and had them put a device on the table next to me and had to breathe through a tube with mist coming out.

Interviewer: *A nebulizer treatment?*

Patient #5: Yeah, I've done that at the doctor's office. A doctor has never been like 'Here, smoke this', I get that. Smoking and vaporization are two very different things however. The fact is, you're going to get medical benefit from using a tincture or topical or edible... but if you want effective results try vaporizing or smoking it.

Interviewer: *Do you have any advice for a patient or provider who might be on the fence about cannabis use?*

Patient #5: Most patients have conditions for which they are prescribed some form of medication right now. I don't know how much people know about the medications they take, but I don't know why people are so willing to go fill a prescription at the pharmacy for a pill they can't pronounce the name of, but they won't try a plant that they literally could grow in their backyard. To me it compares to my grandmother's aloe plant in her bathroom. I mean, you can go to the store and buy a bottle of aloe vera lotion when you get sunburned, but most people had an experience when they were young and got a burn, when their grandmother would go and pinch off a little bit of that Aloe and put it right on the burn. It's not much different than cannabis, you know, it's really not.

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