THE MEDICAL MARIJUANA GUIDE

Cannabis and Your Health

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with DAVE SMITHERMAN

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Introduction

In 1996, California became the first state in the United States to legalize cannabis for medical use. I was practicing pediatrics at a large health maintenance organization in the southern part of the state. There was probably something about it in the news. I think that was the extent of my awareness. I never gave it another thought—until 2015.

Now back on the East Coast and still holding onto my coveted California medical license, I decided to look for some light, part-time telemedicine work. I took my license out of retirement mode and farmed out my curriculum vitae. The first solicitation I received was regarding a pediatric job in San Diego. I explained to the headhunter that I was licensed in California but physically in the Washington, DC, metropolitan area and was not interested in relocating. I would only consider a telemedicine job, perhaps an urgent-care or after-care position.

A few days later, I received another e-mail. It emphatically reassured me that this was a telemedicine job with a new company based in San Francisco. Great, I am interested and excited! As I am reading, looking for the particulars, it goes on to state that the job is to evaluate patients via telemedicine for medical marijuana evaluations. Skreech! What? Marijuana? I don't know anything about marijuana. I tried it a few times in high school and twice as a freshman in college. It made me either goofy, sleepy, or paranoid, so I never thought much of it. I certainly never understood why my peers liked it so much.

So here I am faced with an opportunity to work a few hours a week from my home office with patients in California, and I knew *nothing* about the plant, how it worked, what it was good for, the possible side effects, or how it was dosed; I knew nothing.

Not being one to run from a challenge, I decided to investigate. I interviewed with the president and director of operations. They were clean cut, well spoken, friendly, organized, and professional—not the sleepy-eyed, counterculture stereotypes one might imagine. It was a brand-new company, and except for their chief medical officer, I was their first

medical hire.

I spent the next few days reading the California Board of Medicine's guidelines on what conditions qualified and their assurances that I would not get into trouble making these recommendations—via telemedicine, no less. I started to review the illnesses and conditions that were on their list and began a Pubmed search on cannabis and its role in alleviating the symptoms associated with these conditions. (Pubmed is an online database of journal articles from the National Institute of Health Library.) I searched for *marijuana*, and lo and behold, there were more than 34,000 articles on the subject; *cannabinoids* yielded more than 10,000; and *endocannabinoid* turned up more than 11,000!

I started reading and eventually enrolled in an online course on medical cannabis. I attended whatever conferences I could. Armed with a cheat sheet and a strong internet connection, I began my journey into the field of cannabis medicine. Over the course of the year, I evaluated approximately 3,000 patients. My California patients came from all walks of life and all ages. There were college professors, truck drivers, professional chefs, software developers, doctors, computer programmers, housewives, actors, small business owners, attorneys, students, and retired grandparents. They shared with me the reasons they used cannabis, how they used it, when they used it, and how much.

I learned about applying salves topically to ease migraine or arthritis pain and how to steep cannabis tea or milk to sip through the day to improve its pain-relieving effects. Cancer patients with inoperable tumors that had resolved with cannabis use shared their stories. Anxiety patients would carry a vape pen that they could use in case of a panic attack. Patients with sleep problems were getting the best sleep ever by taking a few drops of cannabis oil at bedtime. And one of the most important things I learned from my patients was how they used cannabis without getting stoned. They could treat their symptoms with no mental impairment. I didn't know that was possible. It was an invaluable education.

We know that there may be long-term consequences for recreational users or patients who self-medicate or who use high doses of cannabis over an extended period of time. But these were patients who were using low to moderate doses of cannabis over many years and who were motivated, functioning successfully, and benefiting from its pain-relieving, muscle-relaxing, antianxiety, and mood-stabilizing benefits. There were patients who, much to many people's surprise, had cancers that were no longer

detectable and pain patients who were no longer on opiate medication and were managing their pain with just medical cannabis. At the end of that year, I thought to myself, “This plant is pretty amazing. And more people, patients, and health-care providers should know about it.” It was then that I decided to call the plant by its scientific name and to drop the term *marijuana*, which had been used to stimulate fear and racial bigotry in an effort to make it illegal for financial and political reasons.

There are a lot of books on the market about cannabis—the science and the medicine. Some are geared more for the doctors and scientists, some for patients or consumers, and some for the horticulturalists and processors. There is even more on the internet, much of it geared toward people who use it for THC’s intoxicating effects, but some sites with a more medical focus. There is some very sound information—and other information, not so much. When researching cannabis, it is important to remember that most people who blog or comment about cannabis can only speak for how it affects *them*. They don’t have the experience of evaluating thousands of people, so their perspective is limited and may not pertain to you and how your body may respond.

Around the world, there has been a resurgence in the use of traditional herbal medicines. In Japan and Taiwan, Kampo, a Japanese variation of traditional Chinese medicine, is fully integrated into the health-care system. By 2010, approximately half of the medical doctors in Japan were incorporating herbal medicine into their practice. More than 70 percent of German physicians prescribe herbs. People are looking for safer and more natural approaches to health and well-being, and cannabis is at the forefront of that movement.

Cannabis has been used medicinally for 5,000 years. It has been an illegal substance for only 75 years. Are there risks to using cannabis? A few, but none that are life threatening. The reasons to make it and keep it illegal at the federal level are not based on science or medicine. There are sociopolitical factors that have kept this very complicated and mostly beneficial plant in the juke joints, back alleys, rock concerts, and college dorms.

This book is written for the patient who has never considered using medical cannabis as a treatment alternative and for the health-care provider who has never considered discussing medical cannabis with their patients. It is my hope that, after reading this book, providers (even those who are not able to make official recommendations for their patients) and patients

who would otherwise not even think about the use of medical cannabis will be more comfortable having the discussion and making an informed decision on whether cannabis might help them. If you decide that cannabis might be worth a try, read, ask questions, start low, and go slow, as you explore the healing properties of this ancient, medicinal plant.

Chapter 1

History of Cannabis

The Journey from Medicine to Intoxicant and Back Again

There was a time when American doctors were able to write prescriptions for cannabis extracts, called tinctures, and salves to treat ailments like migraines, parasites, seizures, pain, and melancholy. It was not a perfect medicine. Dosing could be challenging because no one knew exactly why or how it worked, but most of the time it did work. Except for occasions when a patient was given a vial of cannabis tincture that was stronger than expected and experienced the effects of too much Δ-9-tetrahydrocannabinol (THC), it was safe—so safe, in fact, that no one died.

It is important for both patients and health-care providers to have an understanding of the history of cannabis as a medicine and intoxicant and the series of events that led to every type of the cannabis plant, both fibrous and drug type, to be declared an international public menace and relegated to an illegal, black-market, recreational street drug. With some awareness of the politically and financially motivated efforts to remove cannabis from the physician's toolbox, I think you just might have a better appreciation for this effective and remarkably safe medicinal.

AGRICULTURAL BEGINNINGS

Although human beings emerged about 250,000 years ago, according to archeological evidence, agriculture is a relatively modern invention, at only about 12,000 years old, with some tantalizing evidence of plant cultivation as early as 23,000 years ago.[1] Prior to cultivation, humans were hunters and gatherers, foraging wild berries and plants and following the migratory paths of wild animals. Cultivation was one of the first things that set man apart from other creatures inhabiting the earth. It was man's first attempt at manipulating the environment to suit his needs, and it was the necessary first step toward many technological advances.

Cannabis is certainly one of the first, and perhaps the oldest, cultivated

plant, and it played an important role in mankind's beginnings. Cannabis hemp cord was identified in pottery in a Taiwanese village site dating back at least 10,000 years. Cannabis seeds and oil were used for food in China as early as 6,000 BC, and 4,000 years before the birth of Christ, hemp fibers were used for textiles in China and Turkestan.[2]

ANCIENT MEDICINE

Cannabis, called má, is one of the 50 fundamental herbs of Chinese medicine. Pharmacologist Emperor Shen Nung wrote a book on treatment methods in 2737 BC, which included the medical benefits of má. The *Pen Ts'ao Ching*, written in 1 AD, is based on traditions from the time of Shen Nung and is the oldest known pharmacopoeia. Cannabis was recommended for more than 100 conditions, including gout, malaria, poor memory, and rheumatism.

Hua Tuo (140–208 AD) is credited with being the first healer to use cannabis as an anesthetic. He mixed pulverized cannabis plants with wine and acupuncture to locally and systemically anesthetize patients for wound cleaning and pain control.[3]

In 1993, a 2,500-year-old mummy was discovered in the permafrost of Ukok Plateau in the Altai Mountains of eastern Russia near the Chinese border, an especially cold and dry region. With the inadvertent help of grave robbers, whose disturbance of her tomb allowed water to enter and freeze, the Siberian Ice Maiden (also known as the Princess of Ukok) was so well preserved that even her elaborate tattoos were intact. Anthropologists were able to ascertain what medical conditions she suffered from. MRI scans revealed that the young woman had a malignant tumor in the right breast, with metastasis to the right axillary lymph nodes and spine. The scans also showed that she suffered from osteomyelitis, an infection in the bone, and a skull fracture and other injuries, including a dislocated right hip, consistent with possibly falling off a horse.

This 20-something-year-old was obviously a person of significant stature and prestige. Her coffin was elongated to accommodate a three-foot headdress. Also in the burial chamber (or kurgan, of the Pazyryk culture) were two small tables with serving trays holding horsemeat, mutton, yogurt, coriander seeds, a beverage—and a pouch containing cannabis.[4] While we don't know for sure that she used cannabis to control the excruciating pain she must have experienced, it's highly likely that she

did.

There has been much debate over a passage in the Old Testament in which God gives Moses the recipe for holy anointing oil, often translated as "sweet calamus." Exodus 30:23–25 reads,

> Take thou also unto thee principal spices, of pure myrrh five hundred shekels, and of sweet cinnamon half so much, even two hundred and fifty shekels, and of *kaneh bosem* two hundred and fifty shekels. And of cassia five hundred shekels, after the shekel of the sanctuary, and of oil olive an hin. And thou shalt make it an oil of holy ointment, an ointment compound after the art of the apothecary: it shall be a holy anointing oil.

In 1937, Sula Benet, a Polish anthropologist and professor at Hunter College who specialized in longevity and Eastern European culture, wrote that the Hebrew word *kaneh* means both "hemp" and "reed." I also spoke with a physician from the Israeli Ministry of Health, who asserted that *Kaneh-bos* (singular) translates to "aromatic cane" and that, indeed, the Hebrew term *kaneh bosem* found here means "cannabis" and was an ingredient in holy anointing oil.

Ibn Sina (b. 980), the Persian philosopher and scientist, is best known as the physician who wrote *The Canon of Medicine*, probably the most advanced scientific medical textbook available in its day. Written in Arabic, the *Canon* was translated into European languages and was widely used as a reference in Western universities until well into the seventeenth century. *The Canon of Medicine* makes various references to "Kunnabis" in the treatment of ear infections, skin rashes, and inflammation. In addition, it warns of the problem of using too many leaves.[5]

Cannabis (*vijaya* in Sanskrit) is indigenous to India and is found in more than 80 traditional Ayurvedic formulas. It is recognized as a powerful herb with the ability to both heal and poison and is recommended in only very small doses and always in combination with herbs that balance its effects. It is used to treat pain, digestive disorders, and dysentery and to enhance sexuality. It is known to improve digestion; relieve anxiety; and treat glaucoma, swelling, and diabetes. Its dry, hot, and penetrating qualities are said to have a long-term negative impact on reproductive tissue, and "overuse can lead to dry, weak, brittle tissues."[6] In fact, excessive cannabis use can affect sexual hormone production in both men and women and can negatively affect fertility.

The Materia Medica of Indian Herbalism, published in 1841, notes that long-term consequences of cannabis use can include indigestion, tissue depletion, melancholia, and impotence. Excessive doses can cause "mental exaltation, intoxication, a sense of double consciousness, memory loss and gloominess."[7] It is known as a tamasic drug, which means that, if used in excess, it could dull the mind, affect memory, and cause spiritual confusion. In Ayurveda, the patient is discouraged from smoking because the qualities of smoke are heating, penetrating, and drying. They are encouraged to use cannabis as an edible and along with other herbs or foods to make it less damaging. It is thought that milk balances the negative qualities of cannabis. Traditionally bhang, a cannabis milkshake consumed during certain Hindu festivals, is made by boiling leaves in milk with dates, sugar, saffron, cardamom, rose petals, and almond meal.

WESTERN MEDICINE

Dr. William Brooke O'Shaughnessy (b. 1809) was an Irish physician, surgeon, and chemist who, in addition to his work with cannabis, would later lay the groundwork for intravenous fluid and electrolyte replacement in the treatment of cholera. After graduating from the University of Edinburgh in 1829, he joined the British East India Company in 1833 and moved to Calcutta. There, he served on the committee of the Materia Medica and later as chemical examiner, developing methods for forensic studies to detect arsenic poisoning and other botanical poisons. He was a member of the Medical and Physical Society of Calcutta, where he published one of his first papers on the medical application of cannabis, "Case of Tetanus, Cured by a Preparation of Hemp (the Cannabis Indica)," in 1839. In 1841, O'Shaughnessy returned to England, where he introduced the use of cannabis to Western (European) medicine.

Dr. O'Shaughnessy wrote of his successful treatment with cannabis in "On the Preparations of the Indian Hemp, or Gunjah," published in the *Provincial Medical Journal*, which included "Their Effects on the Animal System in Health, and Their Utility in the Treatment of Tetanus and Other Convulsive Diseases," "Cases of Rheumatism Treated by Hemp," "Case of Hydrophobia [Rabies]," "Use in Cholera," "Use in Tetanus," and "Case of Infantile Convulsions."[8] I have been particularly taken with Dr. O'Shaughnessy's account of the baby girl with infantile spasms. He meticulously chronicled the condition of the baby and the devastating effects of the constant seizing. His description of how he gradually

increased, or titrated, the dose until her body responded to the medicine parallels much of what parents and cannabis clinicians of today have found. In his article, the infant responds at first, but at a later date, the spasms start again. Again, he administered the cannabis tincture, slowly increasing the dose, but he had to give a lot more than the first time. He marveled that the amount needed by the baby was on par with the dose a much older person had taken during an experiment and that, while that amount was intoxicating to the young adult, it did not appear to have any deleterious effects on the baby. It so beautifully illustrates how each batch of medicine may be slightly different, how younger people appear to tolerate much higher doses than do older people, and how every person responds to cannabis differently—all important things to consider when recommending dosing.

THE NEW WORLD

Hemp was such a valued commodity and had so many uses that it was a required crop in the 13 original colonies. It was used as food and to make cloth and rope. In times of shortage, one could be jailed for failing to grow *Cannabis sativa*.

It was also recognized for its medical benefits and was added to the list of approved drugs and treatments, the US Pharmacopoeia, in 1850. Companies like Eli Lilly, Park Davis, and E. and Wm. S. Merrell produced cannabis tinctures that were commonly prescribed for migraines, melancholia, pain, muscle spasms, and seizures. While it was widely used during the second half of the nineteenth century, it began to fall out of favor with the advent of pharmaceutical tablets like aspirin and morphine, which were much easier to dose. Produced as a tincture (a plant extract in alcohol or oil), it was impossible to know the concentration of the psychoactive component, THC, so it was not uncommon for patients to take too high a dose and suffer the adverse effects—dizziness, mental confusion, anxiety, and paranoia.

TWENTIETH- AND TWENTY-FIRST-CENTURY MEDICINE, REGULATIONS, AND POLITICS

Pure Food and Drugs Act of 1906

During this period, excessive opium and cocaine use was creating

problems with addiction. These substances were used in products from Coca-Cola to bogus patent medicines for coughs, pain, and discomfort associated with tuberculosis to even teething medicine for babies. As the addiction problem grew, medicines thought to be less addicting than morphine, like heroin (later found to be more addicting), were developed and prescribed.[9]

As a result, there was an increased social concern that the public was unknowingly using addictive substances. In 1906, the federal Pure Food and Drugs Act was passed for the purpose of "preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors" and required that the "quantity of any alcohol, morphine, opium, cocaine, heroin, alpha or beta cocaine, chloroform, cannabis indica, chloral hydrate, or acetanilide, or any derivative or preparation of any such substances contained therein" be present on the label.[10] With that, the bottles of cannabis tinctures identified the variety of cannabis, the suggested dose, warnings, and sometimes a skull and crossbones symbol, with instructions on what to do for accidental poisonings. Quite naturally, this was cause for concern for some patients. Around this time, there was also a growing sentiment against any type of intoxicant, including alcohol, and the temperance movement was in full swing. The Eighteenth Amendment was ratified in 1919 and remained in effect for 14 years, until it was repealed in 1933.[11]

William Randolph Hearst and the "Mexican Problem"

Many Mexican laborers and migrant workers used cannabis to relieve stress, without the hangover associated with alcohol. It was also used by the soldiers in Pancho Villa's army during the Mexican Revolution (1910–1920).[12] Newspaper magnate William Randolph Hearst was known to have a particular hatred for Mexicans and Mexican Americans, possibly fueled by the loss of 800,000 acres of timberland to Pancho Villa during the Mexican Revolution. He used his newspapers to portray Mexicans as lazy, violent, marijuana-smoking degenerates who stole jobs from white Americans.[13] After the 1929 stock market crash, Americans were faced with the massive unemployment of the Great Depression, and Hearst's racist propaganda fueled the growing anti-immigrant sentiment by citizens who believed that these foreigners were taking their jobs away.

Prior to the federal ban that occurred in the 1930s, states with larger Mexican populations, like California (1913), Wyoming (1915), Texas

(1919), Arkansas (1923), Iowa (1923), Nevada (1923), Oregon (1923), Washington (1923), Montana (1927), and Nebraska (1927), had made recreational use of cannabis illegal. These laws tended to be specifically targeted against the Mexican American population. The *Butte Montana Standard* reported a legislator's comment: "When some beet field peon takes a few traces of this stuff . . . he thinks he has just been elected president of Mexico, so he starts out to execute all his political enemies."[14]

The Decorticator and the Antihemp Campaign

In 1919, George W. Schlichten patented a newly designed decorticator, a machine that could strip the fiber from any plant without first having to soak the plant. It was the first time hemp could be processed efficiently at an industrial level, and it didn't take long before the potential for hemp to be used in paper and other products on a large scale was realized. Hemp was also used to make canvas, sails, paint, rope, and clothing. In the late 1920s, Lammot du Pont began working on polymers to make plastics like neoprene and synthetic rubber and in 1935 introduced his new synthetic fiber, nylon. It has been speculated that mass-producing products from hemp would seriously affect the value of timberland owned by Hearst and others and the synthetic paints and fibers produced by du Pont.

Harry J. Anslinger and the Federal Bureau of Narcotics

In 1930, Harry J. Anslinger was appointed commissioner of the US Treasury Department's newly founded Federal Bureau of Narcotics by financier, Andrew Mellon, his wife's uncle. Anslinger built his career on alcohol prohibition and enforcement and supported the criminalization of drugs, but prior to 1930, Anslinger had voiced a different assessment of cannabis—that it was not a problem and that it did not harm people.[15] However, some believe that, with the end of alcohol prohibition in 1933, he was in need of a new substance to police and control, so cannabis became the target.

Thus began the campaign of distortions, mistruths, and lies about the effects of cannabis, supported by mass media and the yellow journalism of William Randolph Hearst:

> By the tons it is coming into this country—the deadly, dreadful poison that racks and tears not only the body, but the very heart and soul of every human being who once becomes a slave to it in any of its cruel and devastating forms. . . . Marihuana is a short cut to the insane

> asylum. Smoke marihuana cigarettes for a month and what was once your brain will be nothing but a storehouse of horrid specters. Hasheesh makes a murderer who kills for the love of killing out of the mildest mannered man who ever laughed at the idea that any habit could ever get him.[16]

He, more than any other figure, waged a vigorous, vicious, and racially charged campaign against marijuana. Propaganda around the country included statements like:

> There are 100,000 total marijuana smokers in the United States, and most are Negroes, Hispanics, Filipinos and entertainers.[17]
>
> Marijuana, a weird "jazz weed" frequently used by Mexican drug addicts, is the source of much crime in the Southwest.[18]
>
> A reefer is a cigarette made of marijuana and marijuana is a narcotic weed introduced from Mexico to palliate the jittery nerves of hi-de-do Harlemites—especially, it seems, the nerves of bandsmen.[19]
>
> Marijuana is taken by musicians. And I'm not speaking about good musicians, but the jazz type.[20]

Because there was no scientific or clinical evidence that cannabis was addictive or dangerous, and it did not, at the time, pose any major social problems, what was the motivation? What was it about cannabis that made it such a menace?

In 1931, du Pont started to manufacture neoprene, a synthetic rubber, and then began to work on a synthetic fiber that could replace silk. Nylon was eventually introduced to the market in 1935, and in 1938, du Pont received the patent.[21] There are various theories on the motivation behind Anslinger's frenzied attack on cannabis. Some believe it was driven by racial hatred, plain and simple. Others suspect that he was encouraged by Mellon to remove hemp as a possible competitor to du Pont's new synthetic fiber. There is no proof of any orchestrated conspiracy, but Mellon was also the financier backing du Pont. And others have concluded that it was simply a career move to keep the bureau that so vigorously policed alcohol relevant and, most importantly, funded.

Newspapers continued to write articles characterizing Mexicans as frenzied, violent attackers, fueled by smoking marijuana. A 1935 *Los Angeles Times* article reported, "When a Mexican of the lower class runs amuck, tries to snip off the ears of his wife with the carving knife, cut the

throat of his compadre, and it takes six to eight burly American policemen to get him to jail—when those things happen, I say it is as clear as day that the little chap, who otherwise, would be no stronger than a cat, has been smoking marihuana."[22]

Marihuana Tax Act of 1937

In the 1937 congressional hearings, which would ultimately decide the fate of cannabis as a medicine, there was only one person who testified on its behalf. Dr. William Woodward, legislative counsel for the American Medical Association, began by stating that the word *marijuana* was not recognized by the medical profession, and most did not realize that it was indeed cannabis that was the substance in question. He also challenged the claims that cannabis caused addiction, insanity, violence, and death:

> There is nothing in the medicinal use of Cannabis that has any relation to Cannabis addiction. I use the word "Cannabis" in preference to the word "marihuana," because Cannabis is the correct term for describing the plant and its products. The term "marihuana" is a mongrel word that has crept into this country over the Mexican border and has no general meaning, except as it relates to the use of Cannabis preparations for smoking. It is not recognized in medicine, and I might say that it is hardly recognized even in the Treasury Department.[23]

He went on to explain that cannabis had largely fallen out of favor and was not overprescribed. As medicines like aspirin and morphine were introduced into the US Pharmacopeia, the uncertainties of dosing made prescribing cannabis less popular with the doctors of the era. While they still prescribed it, they were turning more and more to the convenient pills being made available:

> I say the medicinal use of Cannabis has nothing to do with Cannabis or marihuana addiction. In all that you have heard here thus far, no mention has been made of any excessive use of the drug by any doctor or its excessive distribution by any pharmacist. And yet the burden of this bill is placed heavily on the doctors and pharmacists of the country; and I may say very heavily, most heavily, possibly of all, on the farmers of the country.
>
> The medicinal use has greatly decreased. The drug is very seldom used. That is partially because of the uncertainty of the effects of the drug. That uncertainty has heretofore been attributed to variations in the

> potency of the preparations as coming from particular plants; the variations in the potency of the drug as coming from particular plants undoubtedly depends on variations in the ingredients of which the resin of the plant is made up.
>
> To say, however, as has been proposed here, that the use of the drug should be prevented by a prohibitive tax, loses sight of the fact that future investigation may show that there are substantial medical uses for Cannabis.[24]

So what caused an ancient medicinal that was still used in other parts of the world, was added to the US Pharmacopeia in 1850, and was prescribed by Western physicians in England and the United States to be outlawed? Why was this medicinal, effective in treating seizures, chronic pain, melancholia, parasites, asthma, and menstrual cramps, stricken not only from the United States but also from virtually every country on the planet? It was probably not one single thing but a series of events and circumstances that led to the prohibition of cannabis.

While cannabis was found to be an effective treatment for many conditions, physicians and scientists did not know how or why it worked. One thing they did know was that dosing could be an issue. When prescribing the tinctures, it was not uncommon for a patient to experience adverse side effects like dizziness, altered mentation, nausea, vomiting, or excessive sedation. As we now know, the cannabinoid production varies from plant to plant, and ten drops of one batch might be therapeutic, but ten drops of the next batch might have a much higher content of THC and sicken the patient. With pills, doctors were able to prescribe the amount of medication, confident that the dose would not make the patient sick. Thus, the use of medicinal cannabis began to decline, not because it was ineffective or dangerous, but because medications in pill form were more predictable.

The LaGuardia Committee Report

In 1944, New York mayor Fiorello La Guardia consulted with the New York Academy of Medicine. He was well aware of the reports made public by Anslinger, Hearst, and others. What they described with cannabis did not match what he had heard about when serving in Congress. There, he learned of cannabis use by soldiers in Panama, which was described by the Army Board of Inquiry as relatively harmless. At the suggestion of the Academy of Medicine, La Guardia appointed a committee to conduct a

social and scientific investigation of cannabis use. While La Guardia did not advocate cannabis use in excess, he hoped that the report might justify an amendment to existing federal law and that further research be done into the possible therapeutic value of cannabis in treating drug addiction.

The study documented that, under the influence of cannabis, subjects did not display statistically significant changes in behavior, the effects were not always related to the amount used, and that the effects at low doses tended to be opposite the effects at higher doses. It was also noted that subjects showed decreased motivation and objectivity, were less aggressive, and were more self-confident, which was thought to be a function of increased relaxation and disinhibition. It was noted that higher doses were associated with less-desirable effects, including anxiety, paranoia, and nausea. Most interestingly, the study compared the personality traits in chronic cannabis users with subjects who did not use cannabis:

> When the productions of the undrugged marihuana user are studied, certain personality traits which serve to differentiate him from the non-user and from the "average" individual can be discerned. As a group the marihuana users studied here were either inhibited emotionally or turned in on themselves, making little response to stimuli in the world about them. People with this type of personality generally have difficulty adjusting to others and are not at ease in social situations. This withdrawal from social contacts apparently finds little compensatory or sublimating activity elsewhere. These subjects did not have a desire or urge to occupy themselves creatively in a manner that might prove socially useful. They showed a tendency to drift along in passive fashion and gave a good portion of their attention to relatively unimportant matters. These men were poorly adjusted, lonely and insecure. As indicated by their history they seldom achieved good heterosexual adjustment.[25]

This description brings to mind traits noted in patients with Asperger's syndrome, which is a condition on the autism spectrum. It is characterized by impairment in social interaction; poor or nonexistent peer relationships; severe social anxiety; restricted patterns of behaviors; and intense interests in narrow, esoteric subjects. It is more common in males than females. As discussed in chapter 5, several preclinical studies have implicated defects in endocannabinoid signaling and neuroinflammation in the etiology of

autism. I now think of self-medication, not aberrant behavior, when I encounter a patient with a history of early cannabis use.

The committee's conclusions in 1944 contradicted the misinformation propagated in the campaign waged by Hearst and Anslinger. Further, marijuana was used mostly by minorities and was not a nidus for criminal behavior:

> From the foregoing study the following conclusions are drawn:
>
> - Marihuana is used extensively in the Borough of Manhattan but the problem is not as acute as it is reported to be in other sections of the United States.
> - The introduction of marihuana into this area is recent as compared to other localities.
> - The cost of marihuana is low and therefore within the purchasing power of most persons.
> - The distribution and use of marihuana is centered in Harlem.
> - The majority of marihuana smokers are Negroes and Latin Americans.
> - The consensus among marihuana smokers is that the use of the drug creates a definite feeling of adequacy.
> - The practice of smoking marihuana does not lead to addiction in the medical sense of the word.
> - The sale and distribution of marihuana is not under the control of any single organized group.
> - The use of marihuana does not lead to morphine or heroin or cocaine addiction and no effort is made to create a market for these narcotics by stimulating the practice of marihuana smoking.
> - Marihuana is not the determining factor in the commission of major crimes.
> - Marihuana smoking is not widespread among school children.
> - Juvenile delinquency is not associated with the practice of smoking marihuana.
> - The publicity concerning the catastrophic effects of marihuana smoking in New York City is unfounded.[26]

Single Convention on Narcotic Drugs

The Single Convention on Narcotic Drugs of 1961 is an international treaty between 154 nations to prohibit the production and supply of narcotics not licensed for medical treatment and research. Its purpose was

to add synthetic opioids that had been developed since the Paris Convention of 1931, which controlled opium, morphine, heroin, coca, and cocaine. It was here that cannabis was added to the list of internationally controlled substances.[27]

Nixon's War on Drugs

Under President Richard Nixon (1969–1974), Congress passed the Comprehensive Drug Abuse Prevention and Control Act of 1970, which regulates the manufacture, importation, possession, use, and distribution of certain substances.[28] The Controlled Substances Act, Title II of the Comprehensive Drug Abuse Prevention and Control Act, puts drugs into one of five classifications. As schedule levels for medications go up, the theoretical risk of abuse goes down. Schedule I is defined as substances having *a high potential for abuse, no accredited medical use, and a lack of accepted safety*. Cannabis, or marijuana and any substance derived from its flower or leaves, is classified as Schedule I, as are heroin, LSD, MDMA (Ecstasy), mescaline, and peyote. Synthetic THC capsules, the exact same THC molecule found in the cannabis plant, were approved by the FDA and introduced to the market in 1986 as a Schedule II medication. Dronabinol was reclassified in 1999 to Schedule III.[29]

Just like Anslinger, Nixon waged a "war on drugs" based on what appears to be cultural and racial prejudice and misinformation. Dead set on instituting a policy that paid little attention to facts or science, Nixon requested a study that would support his conclusion that the use of marijuana was dangerous and should not be legalized. Former Pennsylvania governor Raymond P. Schafer headed the National Commission on Marihuana and Drug Abuse. Among its members were physicians, bipartisan representation from the US Senate and the House of Representatives, an attorney, a college president, a television producer, a university pharmacy department chairman, and a law school dean.

Instead of finding evidence to support continued prohibition, the commission found that marijuana users were not a threat to society but were, in fact, "timid, drowsy, and passive" and recommended in 1972 that marijuana should be decriminalized. Nixon ignored their findings. Instead, it was opposed in 1974 by the recommendations of a congressional subcommittee chaired by conservative Democrat Senator James Eastland from Mississippi.[30]

In 1994, Dan Baum, a writer for *Harper's Magazine*, reportedly had a

conversation with Nixon's domestic policy adviser, John Ehrlichman:

> You want to know what this was really all about? The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. You understand what I'm saying? We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.[31]

The Obama-Era Enforcement Policies

The Cole Memo was written in 2013 by US Deputy Attorney General James M. Cole and sent to US attorneys. It stated that they should prioritize their focus on cannabis enforcement to distribution to minors and criminal and gang activity. They should also prevent diversion from legal to illegal states, authorized activity from being used as a front for trafficking, drugged driving, growing marijuana on public lands, and use and possession on federal property. Attorneys should refrain from prosecuting state-approved cannabis businesses as long as they comply with their state's cannabis regulations.[32]

As part of the 2014 Farm Bill, legislation was passed legalizing *cannabis sativa* L., the fiber or industrial-type plant with less than 0.3 percent THC. State-licensed growers are allowed to grow, process, and sell products from this plant as part of a state's sanctioned research program. It is through these state programs that online and retail hemp-derived cannabidiol (CBD) products are produced.[33]

Rohrabacher-Blumenauer Amendment

The Rohrabacher-Blumenauer Amendment (also the Rohrabacher-Farr Amendment), first introduced in 2001 by Dana Rohrabacher (R-CA), Maurice Hinchey (D-NY), and Sam Farr (D-CA), forbids the Justice Department from using federal funds to interfere with a state's medical cannabis program. It passed in 2014, after six prior failed attempts as part of an omnibus spending bill. Currently the amendment has to be renewed with each new budget bill.[34]

Attorney General Sessions

In the spring of 2017, former senator and newly appointed attorney general Jefferson Sessions (R-MS) wrote a letter to Congress requesting a repeal of the Rohrabacher-Blumenauer Amendment:

> [It would] inhibit [the Justice Department's] authority to enforce the Controlled Substances Act. I believe it would be unwise for Congress to restrict the discretion of the Department to fund particular prosecutions, particularly in the midst of an historic drug epidemic and potentially long-term uptick in violent crime. The Department must be in a position to use all laws available to combat the transnational drug organizations and dangerous drug traffickers who threaten American lives.[35]

In response to the Sessions letter, Senators Cory Booker (D-NJ), Kristen Gillibrand (D-NY), Mike Lee (R-UT), and Rand Paul (R-KY) reintroduced the CARERS Act, which initially stalled after being introduced in 2015.[36] This bipartisan act would allow the possession, production, and distribution of medical marijuana in states that have legalized it. It would also allow Veterans Administration doctors to recommend it to their patients in those states where it is legal; improve access to cannabis for medical research; and deschedule CBD, the major nonpsychoactive component of the plant.[37]

On January 4, 2018, the attorney general rescinded the Cole Memo.[38] This, according to some, has opened the door to federal policing in states that (1) have medical cannabis programs, where a patient must have a doctor's recommendation to use cannabis legally; (2) have decriminalized cannabis use (it is illegal, but if caught, offenders may have to pay a fine on par with running a red light); and (3) have legalized adult-use recreational cannabis for anyone over the age of 21. As for now, the Rohrabacher-Blumenauer Amendment protects medical cannabis programs that are run in compliance with state regulations but not recreational or adult use. While there are concerns about federal interference from officials and cannabis business owners in states with legalized recreational cannabis and users in states that have decriminalized cannabis use, many believe this move by the Justice Department will serve as motivation for states without formal programs in place to increase their efforts to pass medical cannabis legislation.

SUMMARY

The current historic drug epidemic has nothing to do with cannabis. The rise in drug-related deaths is caused by increased access to opiates and benzodiazepines, the combination that accounts for the majority of prescription drug overdoses—access that begins in the doctor's office when patients are prescribed these medications for chronic pain. For some, their pain has resolved, and the drugs remain in the medicine cabinet for other family members to access; for others, it marks the beginning of addiction. A 2014 study published in the *Journal of the American Medical Association* showed that opiate-related overdose death rates had declined by as much as 24.8 percent in states with legal medical cannabis.[39]

After the 2014 legalization of small amounts of cannabis for recreational use in Colorado, violent crime rates in Denver fell 6.9 percent in the first quarter of 2014 compared to the prior year, and property crime dropped by 11.1 percent. A study published in 2014 by researchers at the University of Texas at Dallas concluded that legalization of cannabis does not correlate with an increase in violent or property crime and may actually reduce it as well as reduce alcohol consumption, which *is* associated with an increase in violent crime. Since the legalization of medical cannabis, marijuana trafficking by Mexican drug cartels has decreased significantly, just as bootlegging disappeared after the end of alcohol prohibition.[40]

It is important for patients and health-care providers to understand that the reasons for cannabis being made illegal were based on, what some would argue, economic and sociopolitical issues, not science and medicine. The energy spent on making and keeping it an illegal, schedule I substance is grossly disproportionate to the adverse effects attributed to the plant.

As of June 2017, cannabis is legal for medical use in 29 states, the District of Columbia, and 2 US territories: Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, the District of Columbia, Guam, Florida, Hawaii, Illinois, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Pennsylvania, Puerto Rico, Rhode Island, Vermont, and Washington. An additional 17 states have restrictive CBD-only laws in effect: Alabama, Georgia, Indiana, Iowa, Kentucky, Mississippi, Missouri, North Carolina, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah,

Virginia, Wisconsin, and Wyoming. Only in two of these, Alabama and Missouri, is it possible to obtain CBD without breaking state or federal law. Nebraska is an industrial hemp state, and residents are allowed to use hemp-derived CBD, but Kansas and Idaho are not, so those residents have no legal access at the state level to cannabis of any kind.

Cannabis is no longer considered a gateway drug. According to the CDC, persons addicted to alcohol are two times more likely to also be addicted to heroin, while those addicted to marijuana are three times more likely. In contrast, individuals addicted to cocaine are 15 times more likely to be addicted to heroin, and those addicted to prescription drugs are 40 times more likely to have a heroin addiction.[41] Alcohol, cocaine (commonly used by ENT and plastic surgeons to control bleeding in the operating room), and obviously prescription drugs are all legal.

Cannabis has anti-inflammatory, analgesic, anxiolytic, antipsychotic, antitumor, antispasmodic, and antidepressant effects. It has been proven effective in treating seizures and neuropathic pain in double-blind, placebo-controlled, multicenter studies, where they can research the effects on large numbers of patients, and neither the patient nor the researcher knows who is being treated with cannabis, in order to remove any bias or preconceptions of the part of patients and researchers. It has a relatively low potential for addiction (6 to 9 percent versus 13 to 18 percent for alcohol). Unlike alcohol, cannabis has a lethal dose so high that it’s impossible for a person to inhale or ingest it, and it has no known long-term health consequences other than possible effects on memory and cognition in heavy users who start at a young age.

One has to ask, Why is this plant schedule I? It is my hope that, as you read about the many benefits of cannabis and its remarkably low toxicity profile and learn how to use it in a manner that is not impairing, you might consider it as a safe and effective alternative or addition to your therapeutic program to achieve better health and well-being.

Chapter 2

Legalization

Before considering whether medical cannabis or even hemp-derived CBD might be right for you, it is important to know if using it in your state is permissible. This chapter presents up-to-date information on the legal status of cannabis globally and in the United States. While this information is accurate and current as of January 2018, it is imperative that you verify the status of medical cannabis for your city, county, state, and country.

With the passing of Prop 215 in 1996, California became the first state in the country to legalize medical cannabis. Since that time, 28 additional states, the District of Columbia, Guam, and Puerto Rico have passed legislation allowing for the use of medical cannabis. In 2001, Canada legalized medical cannabis on a national level and, in an effort to put an end to the black market, will legalize adult recreational use sometime in 2018, joining Uruguay.[1] Mexico recently legalized cannabis with less than 1 percent THC for medical use.[2] Other countries that have legalized cannabis for medical use are Argentina, Australia, Brazil, Chile, Columbia, Croatia, Finland, Germany, Greece, India (in some states), Israel, Italy, Jamaica, Norway, Peru, Poland, Romania, San Marino, Turkey, and Zambia.[3] Spanish physicians can prescribe Cesamet (nabilone) and Marinol (dronabinol) for nausea and vomiting in cancer chemotherapy and Sativex in several diseases. In India, cannabis is used medically in many areas of the country, even though it is not technically legal. In areas where it is banned, it is used for religious ceremonies, seemingly without penalty. A “private member’s bill” introduced to parliament recently seeks to eliminate criminal penalties and regulate a legal cannabis market for medical and recreational use, but nothing has passed yet.[4] New Zealand has approved use of high-CBD/low-THC products.

Countries that have decriminalized cannabis for personal use are Austria, Belgium, Belize, Brazil, Chile, Colombia, Costa Rica, Czech Republic,

Ecuador, Georgia, Germany, Iran, Italy, Jamaica, Latvia, Lithuania, Luxembourg, Malta, Mexico, Moldova, the Netherlands, Paraguay, Portugal, Russia, Slovenia, Spain, Switzerland, Ukraine, and Venezuela.[5] France has not decriminalized cannabis use, but jail time is rarely given to offenders. They have recently lowered fines from €3,750 to €150 to €200 (US$180 to US$250).[6] In Greece, punishment has been softened for those caught with cannabis for personal use, but if convicted, a person can still serve up to five months in jail.[7] Cannabis use is not illegal in Peru, but poor, indigenous, small-time traffickers are often incarcerated.

The US Department of Health and Human Services applied for a patent on cannabinoids as neuroprotectants and antioxidants in 1999 and was granted that patent in 2003. However, cannabis is still Schedule I, deeming it to be of no medical value and with a high potential for abuse. For this reason, medical providers in states with medical cannabis programs are still unable to write prescriptions. Instead, "recommendations" can be made to patients that cannabis "might be beneficial" in alleviating certain symptoms.

The government views all cannabinoids in the plant as Schedule I—not only THC, but also CBD, tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and other nonintoxicating compounds in the cannabis plant. Interestingly, synthetic THC, the same molecule in the plant, is classified as Schedule III and has been available since the 1980s by prescription for the treatment of chemotherapy-induced nausea and vomiting and anorexia associated with HIV and AIDS. It is available for prescription use in the United States, Germany, South Africa, and Australia.

At the World Health Organization convention in late 2017, the United Nations officially recommended that CBD not be scheduled as a drug. As stated by the Expert Committee on Drug Dependence:

> Recent evidence from animal and human studies shows that its use could have some therapeutic value for seizures due to epilepsy and related conditions. Current evidence also shows that cannabidiol is not likely to be abused or create dependence as for other cannabinoids [such as THC, for instance]. The ECDD therefore concluded that current information does not justify scheduling of cannabidiol and postponed a fuller review of cannabidiol preparations to May 2018, when the committee will undertake a comprehensive review of cannabis and cannabis related substances.[8]

Even in states where medical cannabis is legal, it is illegal at the federal level. After the 1996 California law was passed, the federal government, under both Bill Clinton and George W. Bush, attempted to prosecute doctors for discussing medical cannabis beyond its possible benefits and risks. Doctors could state that a patient might benefit from cannabis therapy but were not allowed to discuss with the patient types of cannabis and how to use it. They were not able to inform a patient about the whereabouts of a dispensary. All of this information was considered aiding and abetting, and the doctors stood to lose their medical licenses.

The Ninth Circuit Court issued an injunction against the Department of Justice in 2000, which was appealed by the Bush administration. The appellate court, in *Conant v. Walters,* ruled in 2002 that the government could enforce its own laws but could not make a state change its laws. Judge Alex Kozinski went on to say that patients in federally approved studies and programs "provide compelling support for the view that medical marijuana can make the difference between a relatively normal life and a life marred by suffering." The decision also said that doctors could be prosecuted for actively helping patients acquire illegal drugs but not for giving good-faith medical advice that might enable a patient to acquire marijuana independently.[9]

In a 2009 memorandum issued by Attorney General Eric Holder, the Obama administration urged federal prosecutors to not prosecute people who distributed cannabis for medical purposes in accordance with state law. In 2013, the Department of Justice updated their medical cannabis policy; they expected states to create strong enforcement efforts based on state law and would defer their federal right to challenge legalization laws. They also reserved the right to challenge the states at any time they felt necessary.

Although medical cannabis use may be legal in your state, it is still a federal offense, and being a registered patient does not offer job or housing protection and may impede your ability to own a firearm. While the list of qualifying conditions may have been accurate at the time of publication, states often add conditions to their lists that a physician can approve case by case. Many states have a caveat that allows for physician discretion, so a physician can recommend cannabis for any condition thought to benefit from its use. That often includes conditions like insomnia, anxiety, mood disorder, stress, and depression.

If your condition is not listed specifically, do not be discouraged. If in

doubt, contact your state's medical cannabis program and ask. If they are not able to help you, call or e-mail a recommending provider, briefly describe your condition, and ask if they think you would likely be approved. Again, don't be discouraged if your specific condition is not listed. There is generally some flexibility.

QUALIFYING CONDITIONS

Alaska

Alaska passed Measure 8 in 1998, allowing patients and caregivers to grow up to six plants for medicinal use. Caregivers must be at least 21 years old and have no felony drug convictions. In 2014, Ballot Measure 2 was passed, giving the responsibility of establishing dispensary regulations to the Alcoholic Beverage Control Board, which began issuing licenses for dispensaries in 2016.

Qualifying conditions in Alaska are glaucoma, cancer, and HIV and AIDS. Cannabis may also be used for any chronic or debilitating disease or treatment for such diseases that produces cachexia (wasting syndrome), severe pain, severe nausea, seizures, or persistent muscle spasms. Patients must be certified by a physician licensed in the state and can possess up to one ounce or six plants.

Arizona

Arizona passed Proposition 203 in 2010. Patients can be qualified by a physician via an in-office or telemedicine visit. Patients receive a card that allows them to purchase cannabis from the dispensary or to grow their own plants. Patients or their registered caregivers can possess up to two and a half ounces of cannabis in a 14-day period from a licensed dispensary. If the patient lives more than 25 miles from the nearest dispensary, the patient or caregiver is allowed to cultivate up to 12 plants in an enclosed, locked facility.

Qualifying conditions include cancer, post-traumatic stress disorder (PTSD), glaucoma, HIV and AIDS, hepatitis C, amyotrophic lateral sclerosis (ALS), Crohn's disease, and Alzheimer's disease. Cannabis is also permitted for chronic or debilitating conditions or their treatment that produces one or more of the following: cachexia, severe and chronic pain, severe nausea, seizures (including those characteristic of epilepsy), severe or persistent muscle spasms, and multiple sclerosis.

Arkansas

Arkansas passed Issue 6 in 2016, making it legal for patients with a physician's written recommendation to use cannabis for medical purposes. Patients are allowed to possess up to two and a half ounces of cannabis in a 14-day period. Arkansas began accepting online applications for medical cannabis registry cards in June 2017 and has provisions for visitors from other states who are registered in their state medical cannabis program with conditions that qualify in Arkansas.

Qualifying conditions are cancer, glaucoma, HIV and AIDS, hepatitis C, ALS, Tourette syndrome, Crohn's disease, ulcerative colitis, PTSD, severe arthritis, fibromyalgia, and Alzheimer's disease. Cannabis is also permitted for any chronic or debilitating disease that produces cachexia, peripheral neuropathy, intractable pain, severe nausea, seizures, and severe or persistent muscle spasms.

California

California passed Prop 215 in 1996. Qualifying conditions include cancer, anorexia, AIDS, chronic pain, spasticity, cachexia, persistent muscle spasms (including those associated with multiple sclerosis), seizures (including but not limited to those associated with epilepsy), severe nausea, glaucoma, arthritis, migraines, and any other chronic or persistent medical symptom that substantially limits the ability of the person to conduct one or more major life activities (as defined by the Americans with Disabilities Act of 1990) or, if not alleviated, may cause serious harm to the patient's safety or physical or mental health. In truth, qualifying conditions in California are quite liberal. It allows for any condition the physician feels might benefit from cannabis therapy. Recommendations can be obtained by telemedicine, and there is no state residency requirement, although many dispensaries require that the patient have a California state-issued ID. To obtain a recommendation in California, the only requirement is that the patient has to physically be in state at the time of the evaluation. This makes it possible for business and vacation travelers to have access to medication while in the state.

Colorado

Colorado passed Amendment 20 in 2000. Qualifying conditions to become a medical marijuana patient in Colorado include cancer, glaucoma, HIV

and AIDS, and PTSD. Also qualifying are chronic or debilitating diseases or medical conditions that produce one or more of the following: cachexia, persistent muscle spasms, seizures, severe nausea, and severe pain.

Connecticut

Connecticut passed Public Act No. 12-55, an Act Concerning the Palliative Use of Marijuana, in 2012.[10] Qualifying conditions to become a medical marijuana patient in Connecticut include cancer, glaucoma, HIV and AIDS, Parkinson's disease, multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, Crohn's disease, PTSD, sickle-cell disease, postlaminectomy syndrome with chronic radiculopathy, severe psoriasis and psoriatic arthritis, ALS, ulcerative colitis, complex regional pain syndrome (CRPS), cerebral palsy, cystic fibrosis, terminal illness requiring end-of-life care, uncontrolled intractable seizure disorder, and hydrocephalus with intractable headaches. Pending approval by the legislature, cannabis can be used to treat intractable headache syndromes, neuropathic facial pain, spasticity or neuropathic pain associated with fibromyalgia, muscular dystrophy, postherpetic neuralgia, and severe rheumatoid arthritis. For underage patients, qualifying conditions include cerebral palsy, cystic fibrosis, irreversible spinal cord injury with objective neurological indication of intractable spasticity, severe epilepsy, terminal illness requiring end-of-life care, uncontrolled intractable seizure disorder, and muscular dystrophy.

Delaware

Delaware passed SB 17 in 2011. Qualifying conditions to become a medical marijuana patient in Delaware include terminal illness, cancer, HIV and AIDS, decompensated cirrhosis, hepatitis C, ALS, Alzheimer's disease, PTSD (must be certified by a licensed psychiatrist), intractable epilepsy, and autism with self-injurious or aggressive behavior. Also qualifying are chronic or debilitating diseases or medical conditions that produce one or more of the following: cachexia; severe, debilitating pain that has not responded to prescribed medication in three months; intractable nausea; seizures; and severe or persistent muscle spasms, including those characteristic of multiple sclerosis.

If the qualifying patient is younger than 18 years of age, the physician must be a pediatric neurologist, pediatric gastroenterologist, pediatric

oncologist, or pediatric palliative care specialist. Conditions include intractable epilepsy or a chronic or debilitating disease or medical condition that has failed treatment and involves one or more of the following symptoms: cachexia; intractable nausea; and severe, painful, and persistent muscle spasms.

District of Columbia

District of Columbia passed Initiative 59 in 1998. It was overturned by Congress, and in 2010 L18-0210 was passed. Qualifying conditions to become a medical marijuana patient in Washington, DC, include HIV and AIDS, cancer, glaucoma, severe or persistent muscle spasms (including those characteristic of multiple sclerosis), and any other condition that is chronic and cannot be effectively treated by ordinary medical measures or for which medical marijuana would be beneficial, as determined by the patient's physician. DC recently gave nurse practitioners the authority to make recommendations.

Florida

Florida passed Amendment 2 in 2016. Qualifying conditions to become a medical marijuana patient in Florida include cancer, epilepsy, glaucoma, HIV and AIDS, PTSD, ALS, Crohn's disease, chronic seizures, Parkinson's disease, and multiple sclerosis. Cannabis can also be used to treat medical conditions of the same kind or class as or comparable to those listed here, a terminal condition diagnosed by a physician other than the qualified physician issuing the certification, and chronic malignant pain.

Guam

Guam passed Proposal 14A, the Joaquin Concepcion II Compassionate Cannabis Use Act of 2013 in 2014, designated Public Law 32-237 and signed into law on February 16, 2015. It allows the use of medical cannabis for patients with cancer, epilepsy, glaucoma, HIV and AIDS, multiple sclerosis, PTSD, rheumatoid arthritis or similar chronic autoimmune inflammatory disorders, spinal cord injury or other conditions that cause intractable spasticity, hospice care, and a condition for which a patient's practitioner has determined that the use of medical cannabis may provide relief. It allows patients to possess up to two and a half ounces of cannabis flower purchased from a state-licensed dispensary.[11] In February

2018, Public Law 34-80 was passed, establishing much-needed rules and regulations and, among other things, removing the residency requirement to open the program to visitors.[12] However, to date, Guam's medical cannabis program is still not operational.

Hawaii

Hawaii passed SB 862 in 2000. Qualifying conditions to become a medical marijuana patient in Hawaii include cancer, chronic pain, Crohn's disease, epilepsy, glaucoma, HIV and AIDS, lupus, multiple sclerosis, PTSD, and rheumatoid arthritis. Also qualifying for medical cannabis are chronic or debilitating diseases or medical conditions that produce one or more of the following: cachexia, severe pain, severe nausea, seizures (including those characteristic of epilepsy), and severe and persistent muscle spasms (including those characteristic of multiple sclerosis).

Illinois

Illinois passed Public Act 98-0122, the Compassionate Use of Medical Cannabis Pilot Program Act, in 2013[13] and wins the prize for having one of the lengthiest lists of qualifying conditions. The list includes agitation of Alzheimer's disease, ALS, Arnold-Chiari malformation, cachexia, cancer, causalgia, chronic inflammatory demyelinating polyneuropathy, Crohn's disease, CRPS type I and type II, dystonia, severe fibromyalgia, fibrous dysplasia, glaucoma, hepatitis C, HIV and AIDS, hydrocephalus, hydromyelia, interstitial cystitis, lupus, multiple sclerosis, muscular dystrophy, myasthenia gravis, myoclonus, nail-patella syndrome, neurofibromatosis, Parkinson's disease, postconcussion syndrome, PTSD, reflex sympathetic dystrophy, residual limb pain, rheumatoid arthritis, seizures (including those characteristic of epilepsy), Sjogren's syndrome, spinal cord disease (including but not limited to arachnoiditis) and spinal cord injury (with objective neurological indication of intractable spasticity, spinocerebellar ataxia, syringomyelia, and Tarlov cysts), Tourette syndrome, traumatic brain injury (TBI), and terminal illness with diagnosis of six months or less.[14]

Maine

Maine passed Question 2 in 1999, LD 611 in 2002, Question 5 in 2009, LD 1811 in 2010, and LD 1296 in 2011. Qualifying conditions to become a medical marijuana patient in Maine include cancer, glaucoma, HIV and

AIDS, hepatitis C, ALS, Crohn's disease, Alzheimer's disease, PTSD, and nail-patella syndrome. Also qualifying are chronic or debilitating diseases or medical conditions that produce one or more of the following: cachexia, severe nausea, seizures, and severe muscle spasms. Maine grants visitor certifications to patients from other states for up to one year. The patient's home doctor can obtain the forms from the Maine Department of Health.

Maryland

Maryland passed HB 702 (2003); SB 308 (2011); HB 180/SB 580 (2013); HB 1101, Chapter 403 (2013); SB 923 (2014); and HB 881 (2014), similar to SB 923. After four years, dispensaries opened. Qualifying conditions to become a medical marijuana patient in Maryland include cachexia, anorexia, chronic pain, severe nausea, seizures (including those characteristic of epilepsy), severe and persistent muscle spasms, glaucoma, PTSD, and other conditions that might benefit from cannabis. Maryland has the most versatile list of providers allowed to make recommendations: doctors of medicine (MDs), osteopathic doctors (DOs), naturopathic doctors (NDs), chiropractors (DCs), nurse practitioners (NPs), podiatrists (PDs), dentists (DDSs), and midwives.

Massachusetts

Massachusetts passed Question 3 in 2012. Qualifying conditions to become a medical cannabis patient in Massachusetts include cancer, glaucoma, HIV and AIDS, hepatitis C, ALS, Crohn's disease, Parkinson's disease, multiple sclerosis, and other debilitating conditions as determined in writing by a qualifying patient's certifying physician.

Michigan

Michigan passed Proposal 1, also known as the Michigan Medical Marihuana Act, in 2008. Qualifying conditions include cancer, glaucoma, HIV and AIDS, hepatitis C, ALS, Crohn's disease, Alzheimer's disease, nail-patella syndrome, cachexia, severe and chronic pain, severe nausea, seizures, severe and persistent muscle spasms, and PTSD. The law allows for patients or their caregivers to possess up to 12 plants or two and a half ounces of usable cannabis. An MD or DO must write a letter stating that, in their professional opinion, the patient is likely to benefit from cannabis therapy. This letter, an application, and a fee of $100 is submitted to the Michigan Department of Community Health with the Department of

Licensing and Regulatory Affairs. In 2012, the bill was amended to address registration requirements, the definition of bona fide doctor–patient relationships, and proper storage of cannabis medicine during transport. In 2016, HB 4210 was passed to clarify that patients could possess cannabis extracts and infused products.

Minnesota

Minnesota passed SF 2471, chapter 311, in 2014. Minnesota does not allow edibles and concentrates. Qualifying conditions to become a medical marijuana patient in Minnesota include cancer and associated chronic pain, nausea and severe vomiting, cachexia, glaucoma, HIV and AIDS, ALS, Tourette syndrome, seizures (including those characteristic of epilepsy), inflammatory bowel disease (including Crohn's disease), severe and persistent muscle spasms, terminal illness with life expectancy of less than one year, intractable pain, and PTSD. Intractable pain is defined as a

> state in which the cause of the pain cannot be removed or otherwise treated with the consent of the patient and in which . . . no relief or cure of the cause of the pain is possible, or none has been found after reasonable efforts. Reasonable efforts for relieving or curing the cause of the pain may be determined on the basis of, but are not limited to, the following:
>
> 1. When treating a non-terminally ill patient for intractable pain, evaluation by the attending physician and one or more physicians specializing in pain medicine or the treatment of the area, system, or organ of the body perceived as the source of the pain; or
> 2. When treating a terminally ill patient, evaluation by the attending physician who does so in accordance with the level of care, skill, and treatment that would be recognized by a reasonably prudent physician under similar conditions and circumstances.[15]

Montana

Montana passed Initiative 148 in 2004, SB 423 in 2011, and Initiative 182 in 2016. Qualifying conditions to become a medical marijuana patient in Montana include cancer, glaucoma, HIV and AIDS, cachexia, severe or chronic pain, intractable nausea or vomiting, epilepsy or an intractable seizure disorder, multiple sclerosis, Crohn's disease, painful peripheral neuropathy, a central nervous system disorder resulting in chronic and

painful spasticity or muscle spasms, admittance into hospice care, and PTSD.

Nevada

Nevada passed Question 9 in 2000. Qualifying conditions to become a medical marijuana patient in Nevada include AIDS, cancer, glaucoma, PTSD, cachexia, a condition or treatment for a medical condition that produces cachexia, persistent muscle spasms (including multiple sclerosis), seizures (including epilepsy), severe nausea, and severe pain. Nevada allows physician evaluations by telemedicine.

New Hampshire

New Hampshire passed HB 573 in 2013. Qualifying conditions to become a medical marijuana patient in New Hampshire include cancer, Ehlers-Danlos syndrome, glaucoma, HIV and AIDS, hepatitis C, ALS, muscular dystrophy, Crohn's disease, multiple sclerosis, chronic pancreatitis, spinal cord injury or disease, TBI, epilepsy, lupus, Parkinson's disease, Alzheimer's disease, ulcerative colitis, and PTSD. Other qualifying conditions include severely debilitating or terminal medical conditions that produce one or more of the following: elevated intraocular pressure, cachexia, severe pain, severe nausea and vomiting, seizures, and severe and persistent muscle spasms.

New Jersey

New Jersey passed S119 in 2010.[16] Qualifying conditions to become a medical marijuana patient in New Jersey include ALS, multiple sclerosis, cancer, muscular dystrophy, IBD (including Crohn's disease), terminal illness if the physician has determined a prognosis of less than 12 months of life, seizure disorder (including epilepsy), intractable skeletal muscular spasticity, glaucoma, PTSD, severe or chronic pain, severe or chronic nausea or vomiting, cachexia, and HIV and AIDS.

New Mexico

New Mexico passed SB 523 in 2007. Qualifying conditions to become a medical marijuana patient include ALS, cancer, Crohn's disease, epilepsy, glaucoma, hepatitis C currently receiving antiviral treatment, HIV and AIDS, Huntington's disease, hospice care, inclusion body myositis, inflammatory autoimmune-mediated arthritis, intractable nausea or

vomiting, multiple sclerosis, damage to the nervous tissue of the spinal cord with intractable spasticity, painful peripheral neuropathy, Parkinson's disease, PTSD, severe chronic pain, severe anorexia, cachexia, spasmodic torticollis (cervical dystonia), and ulcerative colitis.

New York

New York passed A6357 in 2014. Qualifying conditions to become a medical marijuana patient in New York include cancer, HIV and AIDS, ALS, Parkinson's disease, multiple sclerosis, spinal cord damage with intractable spasticity, epilepsy, inflammatory bowel disease, chronic inflammatory demyelinating polyneuropathy, neuropathies, Huntington's disease, PTSD, cachexia, severe and debilitating pain, chronic pain, severe nausea, seizures, and severe or persistent muscle spasms. Patients can receive their physician's certification in office or via telemedicine.

North Dakota

North Dakota passed Measure 5 in 2016. Qualifying conditions for the North Dakota Compassionate Care Act include cancer and its treatments, HIV and AIDS, hepatitis C, ALS, PTSD (which must be diagnosed by a licensed psychiatrist), Alzheimer's disease and dementia (or treatment of these conditions), Crohn's disease, fibromyalgia, spinal stenosis, chronic back pain (including neuropathy or damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity), glaucoma, and epilepsy. Other qualifying conditions include chronic or debilitating diseases, medical conditions, or treatments that produce one or more of the following: cachexia; severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than three months or for which other treatment options produced serious side effects; intractable nausea; seizures; and severe or persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis.

Ohio

Ohio passed HB 523 in 2016 and is expected to be operational by fall 2018. Qualifying conditions to become a medical marijuana patient in Ohio include AIDS and HIV, ALS, Alzheimer's disease, cancer, chronic traumatic encephalopathy, Crohn's disease, epilepsy or other seizure disorders, fibromyalgia, glaucoma, hepatitis C, IBD, multiple sclerosis,

chronic and severe or intractable pain, Parkinson's disease, PTSD, sickle-cell anemia, spinal cord injury or disease, Tourette syndrome, TBI, and ulcerative colitis.

Oregon

Oregon passed the Oregon Medical Marijuana Act in 1998 and SB 161 in 2007. Qualifying conditions to become a medical marijuana patient in Oregon include cancer, glaucoma, degenerative or pervasive neurological condition, HIV and AIDS, and any medical condition that produces one or more of the following: cachexia, severe pain, severe nausea, seizures (including but not limited to seizures caused by epilepsy), persistent muscle spasms (including but not limited to those caused by multiple sclerosis), and PTSD.

Pennsylvania

Pennsylvania passed SB 3 in 2016, which was signed by the governor on April 17, 2016, but the program is not yet operational. Qualifying conditions to become a medical marijuana patient in Pennsylvania include ALS, autism, cancer, Crohn's disease, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, glaucoma, HIV and AIDS, Huntington's disease, IBD, intractable seizures, multiple sclerosis, neuropathies, Parkinson's disease, PTSD, severe and chronic or intractable pain of neuropathic origin or severe chronic or intractable pain in which conventional therapeutic intervention and opiate therapy is contraindicated or ineffective, and sickle-cell anemia.

Puerto Rico

Puerto Rico passed Public Health Department Regulation 155 in 2016. Their program allows patients access to topicals, pills, transdermal patches, oils, and oral drops but not flower. It also offers reciprocity for visitors with medical cannabis cards from their home states.[17] Qualifying conditions include ALS, cancer, HIV and AIDS, multiple sclerosis, Alzheimer's disease, epilepsy, Parkinson's disease, spinal cord injuries, Crohn's disease, fibromyalgia, anxiety disorders, hepatitis C, arthritis, and anorexia.

Rhode Island

Rhode Island passed SB 791 in 2007 and SB 185 in 2009. Qualifying conditions to become a medical marijuana patient in Rhode Island include cancer, glaucoma, HIV and AIDS, hepatitis C, and Alzheimer's disease. Also qualifying are chronic or debilitating diseases or medical conditions that produce one or more of the following: cachexia, chronic pain, severe nausea, seizures, and severe and persistent muscle spasms.

Vermont

Vermont passed SB 76 in 2004, SB 7 in 2007, and SB 17 in 2011. Qualifying conditions to become a medical marijuana patient in Vermont include cancer, multiple sclerosis, AIDS and HIV, Parkinson's disease, Crohn's disease, and PTSD. Also qualifying are chronic or debilitating diseases that produce one or more of the following: cachexia, severe pain, nausea, or seizures.

Washington

Washington passed Initiative 692 in 1998, SB 5798 in 2010, and SB 5073 in 2011. Qualifying conditions to become a medical marijuana patient in Washington include cancer, HIV and AIDS, multiple sclerosis, epilepsy or other seizure disorder, spasticity disorders, intractable pain, glaucoma, Crohn's disease, hepatitis C, chronic renal failure requiring dialysis, TBI, and PTSD. Other conditions and treatments resulting in anorexia, nausea, vomiting, cachexia, appetite loss, cramping, seizures, muscle spasms, or spasticity qualify for medical cannabis recommendations.

West Virginia

West Virginia signed SB 386 into law in 2017. As it is written, the program is limited to tinctures and vaporized concentrate. No flower is allowed. Physicians must have an unrestricted license, be qualified to prescribe controlled substances, and register with the state.

Qualifying conditions are written broadly and include a chronic or debilitating disease or medical condition that results in a patient being admitted into hospice or receiving palliative care or produces severe nausea, seizures, severe or persistent muscle spasms, severe or chronic pain that does not find effective relief through standard pain medication, cachexia, and anorexia. As written, the law includes conditions like cancer, multiple sclerosis, epilepsy, sickle-cell anemia, autoimmune illnesses (Lyme, lupus, arthritis, polymyositis, etc.), connective tissue diseases (like

Ehlers-Danlos syndrome), mixed connective tissue disorder, medication-induced nausea, neuropathic pain, cerebral palsy, and a host of other conditions. While there is no mention of any psychiatric conditions, there is a caveat for conditions that do not fall within the stated guidelines. The commission *may* approve applications that include any other condition that is severe and for which other medical treatments have been ineffective if the symptoms reasonably can be expected to be relieved by the medical use of cannabis. This *might* include conditions that are not associated with pain or spasms, like PTSD, schizoaffective disorder, schizophrenia, severe anxiety, and major depressive disorder.

HIGH CBD/LOW THC

An additional 18 states have limited high-CBD/low-THC programs. This is misleading because some states have approved cannabis but have not provided a way for residents to access the oils within the parameters of the law. Patients in hemp states can legally access CBD oil derived from industrial hemp.

Alabama

Alabama passed HB 61 (Leni's Law) in 2016.[18] This allows for an affirmative defense for patients (or parents or caregivers) who have a debilitating seizure condition and are using a low-THC (less than 3 percent) extract, free of plant material. Interestingly, the University of Alabama participated in the nationwide Epidiolex study, which examined the efficacy of CBD in treating seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome.

Georgia

Georgia SP 16 only allows for the use of low-THC oil (less than 5 percent THC by weight).[19] Qualifying conditions to become a medical marijuana patient in Georgia include cancer (end stage) or when the treatment produces wasting illness or recalcitrant nausea and vomiting, ALS (severe or end stage), seizure disorders related to diagnosis of epilepsy or trauma-related head injuries, severe multiple sclerosis, Crohn's disease, mitochondrial disease, severe Parkinson's disease, severe sickle-cell disease, severe Tourette syndrome, autism spectrum disorder in patients who are at least 18 years of age, severe autism in patients who are less than

18 years of age; epidermolysis bullosa; Alzheimer's disease (severe or end stage), AIDS (severe or end stage), or peripheral neuropathy (severe or end stage).

Indiana

Indiana passed HB 1148 in 2017. The law provides civil immunity for health-care providers who recommend oil with at least 5 percent CBD and no more than 0.3 percent THC for patients as part of a clinical trial for Lennox-Gastaut syndrome, Dravet syndrome, or other epileptic treatment-resistant conditions. Patients can only be selected by a board-certified neurologist.[20]

Iowa

Iowa allows for the use of high-CBD cannabis extracts with less than 3.0 percent THC.[21] Previously, the only qualifying condition to become a medical marijuana patient in Iowa was intractable epilepsy. House File 524, signed by the governor on May 12, 2017, now allows for cancer, Parkinson's disease, untreatable pain, multiple sclerosis with severe and persistent muscle spasms, seizures (including those characteristic of epilepsy), AIDS and HIV, Crohn's disease, ALS. Also qualifying are any terminal illness with a probable life expectancy of under one year and if the illness or its treatment produces one or more of the following: severe or chronic pain, nausea or severe vomiting, and cachexia.

Kentucky

Kentucky's SB 124 allows for the use of low-THC cannabis or industrial hemp-derived CBD oil. Only those who are participating in a clinical trial or expanded access program are legally allowed to possess CBD oil.[22]

Louisiana

Louisiana's SB 271 passed in 2016.[23] Qualifying conditions to become a medical marijuana patient in Louisiana include symptoms related to cancer, glaucoma, spastic quadriplegia, HIV and AIDS, cachexia, seizure disorders, epilepsy, spasticity, Crohn's disease, muscular dystrophy, and multiple sclerosis.

Mississippi

Mississippi's HB 1231 provides affirmative defense for patients with

debilitating seizure disorders using low-THC CBD oil.[24] Mississippi has decriminalized cannabis possession. The first offense of 30 grams or less is punishable by a $100 to $250 fine and a civil summons.[25]

Missouri

Missouri signed into law HB 2238 on July 14, 2014. With this law, intractable seizure patients may use hemp extracts containing at least 5 percent CBD and no more than 0.3 percent THC. The cannabis must be cultivated and the oil processed in the state in licensed facilities and distributed by licensed CBD oil care centers.

North Carolina

North Carolina HB 1220, the North Carolina Epilepsy Alternative Treatment Act, was signed by the governor on July 3, 2014.[26] It was amended in 2015 with HB 766 to remove the requirement that recommending neurologists be affiliated with a pilot study.[27] It exempts patients with intractable epilepsy from criminal penalties for possessing hemp extracts that contain at least 5 percent CBD and less than 0.9 percent THC. The state provides no means for patients to access medicine, other than acquiring it from a state that allows out-of-state patients to access cannabis from their dispensaries.

Oklahoma

Oklahoma HB 2154, signed into law on April 30, 2015, allowed only patients under the age of 18 with a history of seizures and a written recommendation from a physician to use oil with less than 0.3 percent THC. HB 2835 was passed on May 13, 2016, to include adults with spasticity due to multiple sclerosis or paraplegia, intractable nausea and vomiting, or cachexia.[28]

South Carolina

South Carolina passed Julian’s Law in 2014 to allow for FDA-approved clinical trials to treat patients with Lennox-Gastaut syndrome, Dravet syndrome, and other severe forms of treatment-resistant epilepsy. Patients have access to oil with at least 15 percent CBD and no more than 0.9 percent THC.[29]

South Dakota

In 2016, South Dakota attempted to get medical cannabis on a ballot. They gathered 16,631 signatures, surpassing the necessary 13,870 signatures, but Secretary of State Shantel Krebs deemed half the signatures illegal and rejected the proposed ballot measure. After the rejection, complaints were filed stating that the secretary of state didn't do enough to prove the signatures were invalid. As a result, a Health and Human Services Committee sponsored a bill to legalize CBD oil for limited medical purposes. It passed the Senate in February 2016 but failed in the House in March 2016. Governor Dennis Daugaard was against the liberalization of marijuana laws to allow medical marijuana overall:

> I understand the wishes of those who have medical conditions to have medical marijuana as an option for their treatment. At the same time, I also believe that medical marijuana is also the first step toward recreational marijuana and that in some states, medical marijuana and access to medical marijuana has become more than it should be, and in fact, giving opportunities to those who want to use for recreational use, to mimic or falsify a physical condition to give them the privilege of recreational use when their medical condition doesn't really support it. For those reasons, I've not been supportive of liberalization of marijuana laws.[30]

South Dakota did pass SB 95, which added CBD to the list of Schedule IV controlled substances and excluded it from the definition of marijuana, and it was signed by the governor on March 17, 2017.

Tennessee

Tennessee's SB 280 signed by the governor on May 4, 2015, to permit the medical use of CBD oil that contains no more than 0.9 percent THC. The law allows for the oil to be obtained legally in the United States and outside of Tennessee. Two Republican legislators introduced a bill to the House on January 19, 2018, which was passed onto the Senate on January 22, 2018, that would expand access to patients suffering from a wider range of conditions, including cancer, HIV and AIDS, hepatitis C, ALS, PTSD, Alzheimer's disease, severe arthritis, IBD, Crohn's disease, ulcerative colitis, multiple sclerosis, Parkinson's disease, schizophrenia, and a number of chronic or debilitating diseases.[31]

Texas

Texas's SB 339, the Texas Compassionate-Use Act, was signed by the governor on June 1, 2015, which allows patients with seizure disorders that have failed at least two FDA-approved pharmaceuticals to use CBD extracts with up to 0.5 percent THC. The act also provides for the cultivation, processing, and distribution within the state. In Texas, physicians must provide information on dosing and amounts, which is taken to a dispensing organization to be filled. There are only three licensed dispensaries in the state, but patients can order online from the dispensaries; one is planning a home delivery system with no brick-and-mortar store.[32] Only 14 physicians are participating in the program as of January 29, 2018.[33]

Utah

Utah's HB 105 was signed by the governor on March 20, 2014, to allow patients with intractable seizures to possess cannabis extracts that contain at least 15 percent CBD with no more than 0.3 percent THC. Patients have to apply to the health department and demonstrate failure with at least three other treatments. Nothing in the law allows for in-state procession or distribution. A ballot initiative to allow for whole-plant cannabis has been filed for a 2018 vote. If passed, it would allow for the cultivation, processing, and distribution of edibles, extracts, concentrates for vaporization, and topical salves and creams. In an effort to appease a conservative voting population, smoking flower will not be allowed.[34]

Virginia

In 2017, Virginia passed HB 1445 allowing some epilepsy patients access to CBD or THC-A oil. The law was amended on March 9, 2018 by HB 1251 and signed by Gov. Ralph Northam to remove the epilepsy restriction and provide for affirmative defense for possession. This means that if a patient or caregiver is stopped by law enforcement, the certificate, signed by the physician, will serve as their defense for having the oils in their possession.[35]

Wisconsin

Wisconsin passed AB 726 was signed by the governor on April 16, 2014.[36] It allowed patients with seizures to use high-CBD extracts but did not provide a means for patients to obtain the medicine. In 2017, Act 4 was signed and expanded the law to protect patients with conditions other than

just seizure disorders if they have a physician's recommendation.

Wyoming

Wyoming's HB 0032 became effective on July 1, 2015. It allows residents with intractable seizure disorders to use extracts with at least 5 percent CBD and less than 0.3 percent THC, if recommended by a board-certified neurologist licensed in the state. Patients or their caregivers must complete an application, submit proof of residency, and pay a $150 application fee.[37]

NO ACCESS TO CANNABIS MEDICINE

Idaho

In 2015, Idaho's SB 1146, which would have offered some protection to seriously ill citizens using cannabis oils with low THC, was approved by the legislature in a 22–12 vote but was vetoed by the governor. In January 2018, legislation was again introduced to allow residents to use CBD oil for medicinal purposes, if prescribed by a licensed health-care provider. Even if it passes the state legislature, it still has to be signed by the same governor who vetoed it in 2015.[38] Furthermore, Idaho has no hemp legislation that would allow patients to use industrial hemp-based products, so it may not be legal for patients to possess those either.

Kansas

Kansas has no legislation for medical cannabis. Several attempts to legalize cannabis for medical use have been made but failed. In June 2017, the city of Wichita passed a city ordinance eliminating arrest merely for cannabis possession; offenders must appear in court. First-time offenders over the age of 21 can be fined $50 and are not obligated to complete drug-related counseling. The court retains the authority to impose a higher fine of up to $1,000 and six months in jail (reduced from $2,500 and one year in jail). In addition, offenders must pay for state-mandated drug testing, with costs at around $400. There are other stipulations.[39]

Nebraska

Nebraska has no form of medical cannabis. Sixty percent of its citizens believe that medical cannabis should be legal. The state legislature was

presented with LB 622 in October 2017 but failed to take a vote. Currently, possession of one ounce or less is a misdemeanor punishable by a fine of no more than $300. Subsequent convictions for possessing up to an ounce of cannabis are punishable by increasing fines and ultimately a seven-day jail sentence. Nebraska grows hemp, so use of hemp-based products may be legal.

FEDERAL LEGISLATION

As of February 2018, there are several pieces of legislation that have been introduced to Congress:

- **HR 1820, Veterans Equal Access Act:** Introduced by Representative Earl Blumenauer (D-OR) on March 30, 2017, this bill would direct the Secretary of Veterans Affairs to authorize health-care providers to provide recommendations for the veteran's state medical cannabis program.[40] It was promptly referred to the Committee on Veterans' Affairs and then onto the Subcommittee on Health, where it remains. This is Blumenauer's third attempt at getting this type of legislation passed. Prior attempts have died in committee.
- **HR 3530, Industrial Hemp Farming Act of 2017:** Introduced by James Comer (R-KY) in July 2017, this bill would amend the Controlled Substances Act to exclude industrial hemp from the definition of marijuana and for other purposes.[41]
- **S 1764, The Compassionate Access, Research Expansion, and Respect States Act of 2015 (CARERS):** This piece of legislation was introduced in 2015 and reintroduced in the September 2017 by Senator Cory Booker (D-NJ), along with Kirsten Gillibrand (D-NY), Mike Lee (R-UT), and Rand Paul (I-KY). The act, if passed, would reschedule CBD, allow the banks to offer services to legitimate cannabis businesses operating within state regulations, and permit Veterans Administration health-care providers to recommend medical cannabis to their patients.[42]
- **S 1689, Marijuana Justice Act of 2017:** In December 2017, Senator Cory Booker (D-NJ) was joined by Senator Sam Wyden (D-OR) to cosponsor this legislation, which decriminalizes cannabis by removing marijuana from the Schedule of Controlled Substances, removing the prohibition of its import and export, correcting the disparities in which the criminal justice system targets a disproportionate number of African American and low-income citizens for arrest, and lessening harsh

sentences for defendants in these groups. It would retroactively expunge marijuana-based convictions and allow for those incarcerated to petition for release. The bill would also fund HUD grants to communities that have been unfairly targeted with harsher policing and more severe sentencing for job training, reentry services, expenses related to expungement of convictions for marijuana use or possession, public libraries, community centers, programs and opportunities dedicated to youth, and health education programs.[43]

- **S 1008, Therapeutic Hemp Medical Access Act of 2017:** This legislation was introduced by Cory Garner (R-CO) in May 2017 and would amend the Controlled Substances Act to exclude industrial hemp from the definition of marijuana and for other purposes.[44]
- **HR 3391, Medical Marijuana Research Act of 2017:** Introduced by Andy Harris (R-MD) in July 2017, this bill would amend the Controlled Substances Act to make marijuana accessible for use by qualified marijuana researchers for medical and other purposes.[45]

Access to cannabis for medicinal purposes should not be determined by zip code. It is important to keep in mind that elected officials cannot know what your views are if you do not write and call to let them know how you think they should vote. Share with them the benefits of medical cannabis that you or your family members have experienced, and encourage them to vote in a manner that will enable all of our citizens to have access to cannabis medicine without having to uproot and move away from family and friends or fear legal consequences for doing what they feel is best for their health or the health of the people they care for.

Chapter 3

Cannabinoids, Terpenes, and Flavonoids

Previously, societal resistance to medical cannabis was due to the seemingly mysterious compounds and the vastly different responses of patients to treatment. Thanks to in-depth medical and scientific research, we now better understand the healing elements of cannabis contained within its three key components: cannabinoids, terpenes, and flavonoids. With our understanding of each component, we can target varieties of cannabis to treat specific ailments, many without the side effects or mind-altering highs that a lot of patients want to avoid.

If you are considering medical cannabis—or any other treatment, for that matter—you should understand as much as possible before proceeding. It's important to research how a treatment works, why it works, and what it may be able to do for you. Searching on the internet can be challenging and misleading, so this chapter presents some key information and relevant terms to provide you with a clear understanding of the cannabis plant and its active compounds.

This knowledge and lingo will prepare you for discussions with not only your doctor but also dispensary staff. When my patients already have a basic understanding of cannabis, it's much easier for them to understand their particular treatment plans. I am also more confident that they will be able to find the right products. All patients should be fully aware of expectations of medical cannabis before beginning a cannabis program. Patients should understand what cannabis can possibly help and ensure that their doctors have a solid understanding of what they hope to accomplish. Patients often have multiple symptoms, but one may be more problematic for them than another. The beauty of cannabis medicine is that it often addresses multiple problems, but that is not always the case. Being clear about a patient's needs helps doctors to make the right recommendations for cannabinoid ratios and terpene profiles. It also helps the visit to the dispensary to go more smoothly and efficiently because the

patient is empowered to participate in the decision-making process in the event that what is recommended is not available. The patient can then decide what would be a good substitute.

Don’t be intimidated by the medical terms and jargon presented in this chapter. It’s not important to memorize everything, but it will give you some familiarity and context. When you hear these words again, you may be surprised by how much you remember. It took researchers many years to understand cannabis, so you should take advantage of that information. Knowing not only what cannabis can do but also why it does what it does may help your comfort level and answer questions you didn’t even know you had.

The endocannabinoid system (ECS) is a 600-million-year-old signaling system found in many living organisms, from jellyfish-like hydrozoa to human beings.[1] It consists of cell receptors and ligands (substances that attach to the receptors), protein transporters, and metabolic enzymes. Its primary purpose is to create homeostasis, or balance, within the organism. It is thought that deficiencies within this system can lead to chronic illnesses, like migraines, irritable bowel syndrome, fibromyalgia, and other functional conditions.[2]

The system is believed to have more receptors than any other system in the human body, with cannabinoid receptors embedded in cell membranes throughout the body. The two most-studied receptors, CB1 and CB2, are G-protein-coupled receptors and are the most common type of receptor in the body. The G proteins on the cell membrane recognize substances and modulate, among other things, metabolism, pain, appetite, emotion, memory, stress, gastrointestinal motility, fertility, bone growth, and immune function. CB1 receptors are found mostly in the central nervous system, connective tissues, gonads, glands, and organs, and they are the most abundant receptors in the brain.[3] They affect short-term memory, cognition, mood and emotion, motor function, and nociception (how the brain interprets pain signals).[4] CB2 receptors are found mostly in the immune system throughout the body.[5]

There are other types of receptors in the body involved with pain and inflammation that are modulated by cannabinoids.[6] They include the transient receptor potential vanilloid (TRPV) receptors and cytokines, like tumor necrotic factor (TNF), GPR55, and interleukin (IL) receptors.[7] Serotonin (5-HT1a) receptors that are involved in emotions like depression are also activated by cannabinoids.[8]

Substances that attach or activate the ECS receptors are called cannabinoids, and they are primarily from three sources: endocannabinoids made in the body (ligands), phytocannabinoids found only in the cannabis plant, synthetic cannabinoids made in a laboratory. Endocannabinoids function as neuromodulators and retrograde messengers that affect the release of calcium ions, potassium ions, and other neurotransmitters.[9] For example, when pain fibers are activated, the presynaptic cleft releases calcium and glutamate. When these substances reach the postsynaptic cleft, endocannabinoids are synthesized and released to travel back to the presynaptic cleft to shut down the release of those substances, thus stopping the pain signal.[10] Anandamide and 2-AG are the most-studied endocannabinoids, although it is thought that the body produces several others.[11] These compounds modulate metabolism, mood, appetite, bone growth, pain, inflammation, memory, sleep, muscle tone, and immune function.[12] The name *anandamide* comes from the Sanskrit word *ananda*, meaning “joy” or “bliss.” Also known as N-arachidonoylethanolamine, or AEA, anandamide is a fatty acid derived from N-arachidonoyl phosphatidylethanolamine (NAPE), which is formed from arachidonic acid.[13] Unlike some neuromodulators that are produced and stored in small vesicles until they are needed, AEA is not stored in the body but is produced in very small amounts and only at the time when it is needed.[14] Animal studies suggest that the production of anandamide may be influenced by diet.[15] It binds to both CB1 and CB2 receptors. This lipophilic (fat-loving) molecule is transported into the cell, where it is broken down by-hydrolysis into the by-products arachidonic acid and ethanolamine.[16]

Another cannabinoid is 2-arachidonoylglycerol (2-AG), an ester formed from arachidonic acid and glycerol. Its synthesis is dependent on calcium and the activity of the enzymes phospholipase C (PLC) and diacylglycerol lipase (DAGL).[17] Compared to anandamide, it is present at relatively higher levels in the central nervous system and attaches to CB1 receptors.[18] It, too, is transported by carrier proteins into the cell, where it is broken down by hydrolysis.[19]

THE CANNABIS PLANT

Cannabis is a member of the plant family Cannabaceae, making it a cousin of the more commonly encountered plant hops. There are three primary

cannabis species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.[20]

At one time, the physiological effects of cannabis were somewhat predictable, given the species, but this is no longer true due to the extensive crossbreeding that has occurred over the last 40 years. Indicas typically have higher THC, THCV, and CBDV concentrations than sativas and ruderalis. Sativa plants are tall and skinny, and indica plants are short and bushy. Ruderalis plants are short and thin, high in CBD, and very low in THC. They are sometimes used to produce medicinal cannabis and are often crossed with sativas and indicas to increase hardiness and flowering and decrease growing times and THC content.

Cannabis consists of more than 500 compounds. Of those, the phytocannabinoids affect the ECS. Phytocannabinoids interact with terpenes and flavonoids, which are found in other plants throughout nature and contribute to the medicinal and aromatic benefits of plants. Cannabis also contains amino acids, proteins, sugars, enzymes, fatty acids, alcohols, ketones, lactones, steroids, glycosides, and esters.[21] How these elements influence each other is referred to as the "entourage effect," first described in 1997 by Shimon Ben-Shabat and Raphael Mechoulam, the Israeli scientist who first synthesized delta-9 THC in 1965: "Cannabinoids, terpenes, and flavonoids work together in an entourage such that the medicinal impact of the whole plant is greater than the sum of its individual parts."[22] This suggests the plant in its entirety has a greater medicinal impact.

Cannabis is a dioecious plant, meaning that plants are either male or female, unlike some plants that contain both male and female organs. Cannabinoids are concentrated in the sticky resin produced by trichomes, hairlike structures that protrude from the plant. When seen under magnification, they resemble clear mushrooms, with a stalk and a ball on top. The trichomes and resin that contain the cannabinoids are rich in the flowers and leaves of female plants and are relatively sparse on the stalks of the plant. Male plants produce very few trichomes and therefore are of little use for the production of medicine.[23]

There are approximately 144 different phytocannabinoids.[24] The most well studied include cannabigerol (CBG), tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidiovirdin (CBDV), tetrahydrocannabivarin (THCV), cannabichromene (CBC), and cannabinol (CBN). In the raw plant, the cannabinoids exist in an acidic state, and while they have

biological and medical benefits, they are not psychoactive. Cannabigerolic acid (CBGA) is the mother of all cannabinoids. With light, heat, and time, CBGA produces THCA, CBDA, CBCA, and THCVA.

Tetrahydrocannabinolic Acid (THCA)

THCA is the precursor to THC, which is produced if the plant is heated by smoking, vaporizing, or cooking. THCA has anticonvulsant, antispasmodic, anti-inflammatory, neuroprotective, and analgesic properties. It binds to TRPA1 receptors and blocks TRPM8 receptors, which are necessary for the growth of prostate cancer. THCA also binds to GPR55, CB2, and CB1 receptors, but it doesn't cross the blood–brain barrier (a capillary system that prevents certain substances from reaching the brain); therefore, it is nonpsychoactive. It is effective in treating chronic and neuropathic pain; alleviates nausea and vomiting; has antibiotic properties; and has been shown in preclinical studies to interfere with the growth of prostate, breast, rectal, and stomach cancers. Its potent anticonvulsant properties have made it a next-step medicinal when CBD is ineffective.

Cannabinolic Acid (CBDA)

CBDA has anti-inflammatory and antitumor properties, particularly in inhibiting the migration of certain breast cancer cell lines in preclinical studies.[25] It is thought to have higher anti-inflammatory properties than CBD. It does not bind efficiently to CB1 or CB2 receptors but has greater affinity at the 5-HT1A receptor. Part of its anti-inflammatory effect is via the inhibition of the enzyme COX-2.[26] In contrast to the many pharmaceutical COX-2 inhibitors, CBDA is not known to have any cardiac, gastric, or renal toxicity. On the contrary, it has been shown in animal studies to protect these organ systems from oxidative damage. In other studies, CBDA has been found to have significant antiemetic effects.[27] In my clinical experience, I have found preparations containing CBDA to be very effective in treating chronic arthritic pain and pain associated with inflammatory bowel disease.

Tetrahydrocannabinolvirdinolic Acid (THCVA) and Cannabichromenolic Acid (CBCA)

THCVA and CBCA are the precursors to THCV and CBC. While there is not as much research on the actions of these cannabinoids, their neutral

forms are being studied.

When cannabis is heated by smoking, vaporizing, or cooking; is exposed to UV light; or after a period of time, the acidic cannabinoids are neutralized by a chemical reaction called decarboxylation. Decarboxylation imbues some of the cannabinoids—most notably THC and THCV—with psychoactive properties. Tetrahydrocannabivarin (THCV) is psychoactive at higher doses. It is energizing, anxiolytic, and reduces insulin-resistance tremors (the tremors that appear in patients with obese endogenous insulin-resistant diabetes).

Tetrahydrocannabinol (THC)

THC is the major intoxicating cannabinoid in the plant. In addition to its ability to produce a euphoric state of consciousness, it relieves pain; stimulates the appetite; reduces nausea; promotes restful sleep; has antitumor activity; and is a muscle relaxant, an antipsychotic, an antidepressant, and a potent anti-inflammatory.[29] THC binds to CB1 and CB2 receptors in very small amounts. It is a CB1 partial agonist but is also a CB1 and CB2 antagonist.[30] Thus, it can be therapeutic at low to moderate doses but may not be helpful or can make symptoms worse when too much is taken. For example, THC is effective at treating pain with low to moderate doses but relatively ineffective as an analgesic if too high a dose is taken. It can alleviate anxiety and nausea with low doses but can cause anxiety, paranoia, nausea, and vomiting with high doses. THC also potentiates the pain-relieving effects of opiates. This has enormous potential in addressing the side effect and overdose issues associated with opiates. Patients typically get the same or better pain relief with as much as a 75 percent reduction in the opiate dose.

Delta-8 THC binds similarly to CB1 and CB2 receptors but is slightly less psychoactive than delta-9 THC.

Cannabinol (CBN)

Cannabinol (CBN), a by-product of THC, is mildly psychoactive but is thought to dampen the psychoactivity of THC. It is typically found in “old” cannabis and is known to have sedating effects that are useful in treating insomnia.[28]

Cannabidiol (CBD)

CBD is slowly becoming the darling of the cannabinoids. It was first

brought to the public's attention as an alternative treatment for seizures in children. Most people are unaware that CBD also reduces inflammation, relieves neuropathic pain, suppresses appetite, regulates glucose and fat metabolism, interrupts the stress response, relieves anxiety, stabilizes mood, is an antipsychotic, reduces nausea, promotes bone growth, modulates the autoimmune system, is neuroprotective and a potent antioxidant, and has antitumor activity.[31] When present, CBD mitigates the psychoactivity and effects on memory attributed to THC, so patients can use cannabis to alleviate their symptoms while remaining clear-minded and focused.[32]

Other Cannabinoids

CBG is the cannabinoid from which all other cannabinoids are formed. In the mature plant, it is usually only found in very small amounts. CBC is not as well known as THC and CBD but plays an important role in the medicinal effects of the cannabis plant. It is the second-most abundant cannabinoid in varieties of cannabis that do not contain CBD. It is nonpsychoactive and has pain-relieving, anti-inflammatory, antimicrobial, and mood-elevating effects. It also potentiates the anti-inflammatory effects of THC. In preclinical studies, when in the presence of THC and CBD, CBC appears to increase the concentration of stem cells in the brain.[33] This has important implications in researching neuronal regeneration for patients with brain injuries and neurodegenerative disorders.

CBDV has anticonvulsant activity and stimulates osteoblasts, cells that form bone. There may be future implications in the treatment of osteopenia and osteoporosis. While mildly psychoactive, THCV has analgesic properties and is known to suppress appetite. It is being researched as a possible therapy for obesity.

When THC is oxidized, the primary product of degradation is CBN. This cannabinoid attaches to CB1 and CB2 and causes sedation, but it is only very mildly psychoactive. In addition to its antispasmodic and anti-inflammatory effects, it inhibits keratinocyte formation and may play a role in treating psoriasis. Research is being conducted on CBN's possible role in burn management because it activates TRP receptors, which are sensitive to high temperatures. It promotes bone formation and may play a role in bone healing and the prevention and treatment of osteoporosis.

Cannabinoids that are less commonly measured and are not as well

understood include cannabicyclol (CBL), cannabivarin (CBV), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), and cannabigerol monoethyl ether (CBGM).

OTHER COMPONENTS OF THE CANNABIS PLANT

Terpenes are naturally occurring compounds found throughout nature that give plants their medicinal and aromatic qualities. They consist of hydrocarbon units called isoprene and are grouped according to the number of isoprene units in the molecule.[34] For example, monoterpenes contain two units; sesquiterpenes, three; and diterpenes, four. Monoterpenes, sesquiterpenes, and diterpenes are abundant in the essential oils of plants, including cannabis.

Each cannabis variety has a unique mix of terpenes, commonly referred to as the terpene profile, that can vary even among plants from the same seeds and that influences how a particular cannabis variety will impart its therapeutic effect.[35] Terpenes (specifically alpha caryophyllene), and not cannabinoids, are responsible for the unique aroma of cannabis.[36] More than 200 have been found in the plant's trichomes. Terpenes are very sensitive and decrease in quantity with time. Air-dried cannabis that has been stored for as little as a week will lose about 30 percent of its terpenes, and at three months, cannabis can lose more than half of its terpenes.[37] The following terpenes are among those found in cannabis.

Beta-caryophyllene is also found in black pepper, cinnamon, oregano, basil, hops, rosemary, and cloves.[38] It is the dominant terpene in industrial- or fiber-type cannabis and has anti-inflammatory, analgesic, gastrocytoprotective, antimalarial, antitumor, and antispasmodic properties. It has been shown in an animal model to protect kidney cells from chemotherapy-induced inflammation and oxidative stress.[39] Some consider it to be a secondary cannabinoid because it also binds to the CB2 receptor.[40]

Humulene is also found in cloves, basil, and hops and has anti-inflammatory, antitumor, and antibacterial effects.

One of the most common terpenes in nature, limonene, imparts a mood-elevating and calming effect and can alleviate symptoms caused by depression and anxiety.[41] It is also found in the rinds of oranges, lemons, mandarins, limes, and grapefruit.[42] It induces apoptosis, or programmed

cell death, giving it antitumor properties, as well. In preclinical studies of breast cancer, limonene was shown to cause greater than 80 percent of carcinomas to regress. Evidence from a phase l clinical trial showed a partial response to limonene in a patient with breast cancer, and limonene stabilized colorectal cancer in three patients for more than six months.[43] Limonene is cholesterol solvent and has been used clinically to dissolve cholesterol-containing gallstones.[44] It neutralizes gastric acid, supports normal peristalsis, and has been used to relieve gastroesophageal reflux. It has also been shown in animal studies to reverse fatty-acid buildup in nonalcoholic fatty liver disease.[45]

Alpha and beta pinene are the major components of the essential oil of pine trees and gives them their distinctive aroma. Varieties of cannabis that contain pinene may be particularly effective in alleviating symptoms associated with asthma because it facilitates the opening of the airways and decreases inflammation and wheezing. In addition to being a bronchodilator and anti-inflammatory, pinene has antibacterial properties.[46]

More than 200 species of plants produce linalool, which is found mainly in lavender, coriander, mints, laurels, cinnamon, rosewood, citrus, and birch. It is known to reduce anxiety and amplify the mood-elevating effect of THC. It is sedating and often used to treat insomnia. It has anticonvulsant, local analgesic, and anesthetic properties.

Found in hops, mangos, and cloves, myrcene is prominent in most varieties of cannabis. It is sedating and body relaxing and has anti-inflammatory, antispasmodic, and analgesic properties.[47] It is an important component in varieties of cannabis that are known to promote sleep.

Basil, mint, hops, mango, parsley, pepper, and basil are among the many sources of ocimene.[48] Ocimene has antiviral, antifungal, antiseptic, and antibacterial properties and acts as a decongestant.

Terpinolene is found in a variety of other pleasantly fragrant plants, including nutmeg, tea tree, conifers, apple trees, cumin, and lilacs. It is reported to have sedating and antispasmodic effects.

Transnerolidol is found in teas and lemongrass; is sedating; and has antiparasitic, antifungal, and antibacterial properties.

Flavonoids are nutrient-rich pigments found in many plants, vegetables, fruits, and teas. The Latin word for “yellow” is *flavus*; thus, flavonoids are commonly found in yellowish leaves, flowers, and fruits. Flavonoids are widely distributed throughout the plant kingdom and have a broad range of

biological and pharmacological activities. They are potent antioxidants and can also have anti-inflammatory, antiallergy, antimicrobial, antitumor, and cardiovascular benefits. Foods that have high flavonoid content include citrus fruits, teas, berries, parsley, onions, red wine, and dark chocolate. Cannabis contains at least 29 flavonoids, which add to the medicinal benefits of the plant. Historically, cannabis root, which is rich in flavonoids and devoid of cannabinoids, has been used to treat inflammation and pain.

Cannflavin A, cannflavin B, and cannflavin C are found in drug-type cannabis and inhibit cyclooxygenase enzymes and prostaglandin E2 production, making them anti-inflammatory.[49]

B-sitosterol, which is found in many plants, is a 5-alpha-reductase inhibitor and anti-inflammatory.

Apigenin is also found in parsley and celery and is especially plentiful in chamomile. It attaches to benzodiazepine receptors, making it anxiolytic and mildly sedative. It is also anti-inflammatory and estrogenic. Animal studies show that apigenin stimulates neuronal differentiation.[50] Although this effect has not been demonstrated in humans, it may one day prove useful in generating new nerve cells.

Luteolin is widely available in many edible plants, including peppers, parsley, broccoli, celery, thyme, dandelion, perilla, cucumber, capers, turnip, buckwheat sprouts, rooibos tea, chocolate, pomegranate, artichoke, lettuce, carrots, rosemary, peppermint, oregano, chamomile, and olive oil. Preclinical studies have demonstrated that luteolin has antioxidant, antimicrobial, anti-inflammatory, and antitumor effects.[51] Luteolin inhibits COX-2 and other pro-inflammatory enzymes. Preclinical studies have shown luteolin to be effective in suppressing *Chlamydia pneumoniae* growth in inoculated mice, anti-influenza virus activity, and antifungal activity with a potency similar to ketoconazole.[52] Luteolin also demonstrates antiparasitic action against *Leishmania donovani* and *Plasmodium falciparum*.[53] Luteolin's antitumor effects may be a result of its antioxidant properties and its ability to prevent DNA alterations in oncogene, tumor-suppressor, and stability genes. Luteolin may also induce topoisomerase II–mediated DNA alterations, which may indicate possible anticancer activity, but without knowing the effects plant compounds have in high doses, this ability to alter DNA could possibly lead to long-term toxicity if taken in concentrations higher than those found in a plant-based diet.

Orientin is luteolin-derived and also found in passion flower, açaí, and millets. It is an antioxidant, anti-inflammatory, and antimicrobial.

Kaempferol is found in witch hazel and grapefruit and is present in high levels in such cruciferous vegetables as broccoli and cauliflower. It appears to have antidepressant and antitumor properties.

Quercetin is found in onions, green tea, buckwheat tea, apples, berries, gingko, St. John's wort, American elder, and red wine. It has antioxidant and anti-inflammatory properties and has been reported to activate estrogen receptors. It may be effective in reducing the pain and swelling of prostatitis. Some research suggests that quercetin and kaempferol, consumed in high amounts, may reduce the risk of lung and pancreatic cancer, particularly in men who are cigarette smokers.[54]

Flavone glucosides are formed when a flavone combines with a sugar. Vitexin is an apigenin-derived flavone glucoside found in passion flower, chasteberry, hawthorn, and millet. Animal studies show that it has analgesic, antioxidant, antitumor, antiviral, antispasmodic, antithyroid, antidepressant, and cardioprotective properties. Isovitexin, another flavone glucoside made from apigenin, is a free-radical scavenger. It is also found in passion flower and açaí palm.

The compounds in the cannabis plant work together in ways that are not yet clear. Our lack of understanding of how these substances influence each other makes it difficult to predict why some cannabis varieties help alleviate the symptoms of one problem and not another.

Anecdotal experience tells us that patients with pain tend to respond to varieties of cannabis rich in beta-caryophyllene and limonene. Insomniacs respond to myrcene or higher levels of CBN. Patients with seizure disorders often find cannabis plant varieties rich in linalool to be more effective than those without.

The bottom line is that each patient has to experiment with a number of different plant strains to determine what works best for them. When trying different varieties, it's important to record any information that is given—cannabinoid ratios, terpenes, and concentrations.

We have yet to begin testing for flavonoids, and there are probably more compounds to be discovered. Finding the right cannabis variety, as well as the right dose amount, is a process. Take your time, start low, and increase slowly.

SYNTHETIC CANNABINOIDS: SPICE AND K2

Spice, or K2, street drugs known as synthetic marijuana, began to emerge in 2008 in convenience stores and head shops and online.[55] It was also referred to as “legal high,” “potpourri,” and “incense.” *They are not legal or safe*. These drugs consist of plant material chopped up to resemble cannabis and then sprayed with chemicals. The chemicals change from time to time to avoid federal regulation. They are *full* CB1 agonists. THC, both natural and synthesized, is a *partial* agonist of the CB1 receptor. This difference is similar to the difference between turning on a bathtub faucet full blast and a slow drip of melting ice. It has been associated with many emergency department visits and hospitalizations. Adverse effects associated with Spice include hallucinations and psychosis, seizures, heart attack, nausea and vomiting, kidney failure, and death.

PHARMACEUTICAL CANNABINOIDS

Dronabinol, nabiximols (Sativex), and nabilone are synthetic cannabinoids approved by the FDA to treat anorexia and wasting caused by HIV and AIDS and nausea and vomiting caused by chemotherapy in cancer treatments.

When I began my practice in Maryland in 2016, the dispensaries were not yet open. Not only was I evaluating Maryland patients, but I was also seeing a fair number of patients from states without legalized medical cannabis. Patients came to me in Maryland because, initially, Maryland’s regulations did not have a residency requirement. Although the regulations are being reevaluated, it was written such that any patient receiving medical care in the state had access to the program. Patients from other states began coming to Maryland for help. The Maryland Medical Cannabis Commission is now approving out-of-state patients receiving residential or in-patinent care in Maryland.

These patients had debilitating conditions, like severe chronic pain, painful muscle spasms, and tremors. For those patients, I recommended that they begin using a hemp-derived CBD, and for many, that was sufficient in alleviating their symptoms. For others, it was not quite enough. For those patients, I prescribed dronabinol (Marinol). Dronabinol was FDA approved in 1986 for the treatment of anorexia or wasting syndrome due to HIV and AIDS and for intractable nausea and vomiting associated with chemotherapy for cancer. Dronabinol is delta-9 THC. It is the same molecule that is in the cannabis plant. The difference is that in dronabinol, the THC is all by itself. It doesn’t have other cannabinoids,

terpenes, or flavonoids to influence its effects. Therefore, it does not produce a euphoric high and, in fact, can cause some patients to experience dysphoria, or an unpleasant feeling. I liken it to a carrot sitting on a plate, freshly pulled from the ground, versus a carrot-ginger soup made with a seasoned broth, ginger, thyme, salt, pepper, and a dash of sherry. It's the same carrot, same nutrients, but the soup is more appetizing and flavorful. Dronabinol attaches to and activates the cannabinoid receptors in our bodies, so it has the ability to relieve some of the same symptoms as does THC from the plant. Not only does it stimulate the appetite and quell nausea and vomiting, but it also relieves pain and reduces tremors and abnormal movements from Parkinson's and Huntington's diseases.

For patients experiencing excruciating pain and the adverse effects of opiate medication, I began to prescribe small amounts of dronabinol in combination with hemp-derived cannabidiol. And guess what? For most patients, it actually reduced their pain to the degree that they were able to wean off not only the opiates but also the benzodiazepines, anticonvulsants, antidepressants, and muscle relaxants. Some patients, however, were very sensitive to dronabinol and did not like its mind-altering effects, similar to when someone takes too much THC—rapid heart rate, hallucinations, out-of-body sensations, and anxiety. If your health-care provider thinks that a synthetic cannabinoid might help alleviate your symptoms, and if you live in a state where it is legal to use hemp-derived CBD, I recommend taking it in combination with CBD to buffer the adverse effects rather than taking it by itself.

Getting prescription coverage for these medications can be tricky. Some insurance plans cover it. Other insurance companies and Medicare will not cover the charges if the patient does not have anorexia from HIV or severe nausea from chemotherapy. If your insurance company will not cover synthetic cannabinoid and CBD, there are coupons available online that can reduce the cost substantially.

Nabilone is also made in the pharmaceutical laboratory. Unlike dronabinol, it is *similar* to but not the same molecule as THC. It interacts with the ECS and is approved to treat chemotherapy-induced nausea and vomiting.

Nabiximols (Sativex) is a botanical pharmaceutical that was approved for use in the United Kingdom in 2010. It is standardized so that each spray delivers a dose of 2.7 milligrams of THC and 2.5 milligrams of CBD. It is also approved for multiple sclerosis in Austria, Belgium, Czech Republic,

Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Lichtenstein, Luxembourg, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, Canada, Australia, New Zealand, Brazil, Colombia, Chile, the United Arab Emirates, and Kuwait. It is also approved for pain and spasticity from multiple sclerosis and chronic cancer pain in Israel.

Cannabis is an extremely complicated plant. Its many compounds work together in ways we do not fully understand. It can create homeostasis or balance by interacting with the body's endocannabinoid system. When a body's system is not doing the job, cannabinoids, terpenes, and flavonoids from the plant work together, influencing each other in an entourage effect, to mitigate a variety of symptoms and provide relief. Everyone responds to cannabis uniquely, and it is a process to figure out what works best for you and your symptoms. THC has a lot of benefits, but it doesn't help everything and probably works best when CBD is onboard as well. Take your time. Try different varieties. Keep records. Use your knowledge of what cannabinoids and terpenes can do, and with patience, you can personalize your medicine.

Chapter 4

Laboratory Testing

Cannabis itself is a very safe plant, and no one has ever died from a cannabis overdose. However, it is a plant, and plants can be diseased or contaminated with such biologicals as mold, bacteria, and toxins, which are poisons produced by organisms that grow on the plant. They can also contain chemicals, like heavy metals, residual solvents from processing techniques, or pesticides. Cannabis products from the dispensary should be tested not only for cannabinoid and terpene profiles but for all of these possible contaminants as well.

INFESTATION

When mold spores on the plant are inhaled, they are deposited in the lungs, where they can cause infection. A patient with an intact immune system will most likely fight off any infection, but those whose immunity is compromised, like patients with AIDS or those receiving chemotherapy, are at risk of developing infection—which can be deadly.

Two Northern California patients undergoing chemotherapy and using medical cannabis developed rare fungal infections. One patient, who was also receiving stem-cell treatments, was nebulizing medical cannabis in an aerosol to alleviate the nausea and vomiting associated with the chemotherapy. He subsequently died from the infection.

When specimens from several California dispensaries were tested, they were found to be contaminated with multiple bacteria—*Klebsiella*, *Pseudomonas*, *E. coli*, *Acinetobacter*, and *Stenotrophomonas*.[1] While the heat from smoking cannabis might have killed the fungus, it is not guaranteed that all of the microbes will die. Ingestion of alcohol-based tinctures and cooked products might be a safer alternative for at-risk patients.

Until this year, laboratory-testing requirements in California varied from

county to county. Beginning January 1, 2018, the California Medical Cannabis Regulation and Safety Act, passed in 2015, went into effect, creating a comprehensive state-licensing system for commercial cultivation, processing, retail sale, transport, distribution, delivery, and testing of medical cannabis.[2]

TOXINS

Aflatoxins are poisonous substances produced by the mold *Aspergillus*. These toxins can contaminate agricultural products like corn, peanuts, and grains during production, harvest, or storage. Highly toxic to the liver, exposure to aflatoxins is also associated with the development of liver cancer.[3]

RESIDUAL SOLVENTS

Concentrates are made by carbon dioxide extraction or by using a variety of light hydrocarbon solvents, like butane, hexane, and propane. Not only are the cannabinoids and terpenes concentrated, but any pesticides on the plant will be concentrated as well. In carbon dioxide extraction, pressure and temperature are used to turn the carbon dioxide gas into a liquid. That liquid is then used to extract the plant's medicinal compounds.

Butane, hexane, and propane are also used to extract the medicinal components from the plant. This method of extraction, better at concentrating not only the cannabinoids but also the terpenes (which may not be extracted as efficiently by safer methods like carbon dioxide extraction) makes high-quality and highly pure medicine and can be very safe and effective if the solvent is removed properly.

These solvents are often used because the extraction method is cheaper, but it is very important to remove the residual solvents from these concentrates before they are used in cannabis medicine for ingestion or inhalation. This additional step requires close monitoring and state-of-the-art equipment, which increases the processor's cost, so many unscrupulous businesses skip it in order to increase their profit margins.[4]

CANNABINOIDS AND TERPENES

The labs typically test for ten cannabinoids: delta-9 THC, THCV, CBD, CBDV, CBG, CBC, CBN, CBGA, CBDA, and THCA. They report the

percentage of each cannabinoid found in the plant, usually 4 or 5 percent. Once the product is labeled for the patient, it usually lists the concentrations of CBD, THC, and sometimes CBN or CBG. Labs test for a larger variety of terpenes, around 30 to 40, in the plant than cannabinoids, but they are found in much lower concentrations and generally yield about 8 to 10. The terpene concentrations are usually about 1 to 3 percent in the flowers but can be as high as 8 percent in concentrates.[5]

PESTICIDES AND HEAVY METALS

Cannabis is an environmental cleaner. It absorbs pesticides and heavy metals, like cadmium, arsenic, mercury, and lead found in the air, soil, and water. For cannabis grown in soil outdoors, any pesticide residue in the soil from prior crops can be absorbed into the plant, even if the chemicals are not actively used to prevent infestation of cannabis. While there are some legitimately pesticide-free cannabis growers, for the most part, when cannabis is grown outside of state regulatory guidelines, the plants are typically laden with pesticides. The clone or starter plant is often dipped in pesticide and then is sprayed every week or so, whether there are any signs of infestation or not. Furthermore, because cannabis is not a USDA-recognized crop, there are no pesticides approved for use on cannabis plants.

In 2016, a Northern California cannabis testing lab found that 84 percent of the medical cannabis samples tested positive for large amounts of pesticides. More than 65 percent of the samples were positive for myclobutanil, the active ingredient in Eagle 20. This pesticide is particularly effective in treating powdery mildew, a fungal disease that affects a number of plant varieties, including cannabis. When burned, myclobutanil turns into hydrogen cyanide.[6] Cyanide is known to have deleterious effects on the brain, nervous system, and heart.

The state of Colorado allows for the use of pesticides in cannabis cultivation, but the pesticides must be used in accordance with its labeled directions. The label must allow for use on unspecified crops or plants, for use at the site (e.g., greenhouse vs. outdoors), and for use on crops for human consumption.[7] The problem with this is that there is a difference between consumption and inhalation, and for patients who smoke or vaporize, it is not known if there are any adverse effects.

WHAT ABOUT ORGANIC?

Technically speaking, cannabis cannot be certified organic because of its federal status. The US Department of Agriculture does not recognize it as a legitimate crop, it cannot be USDA-certified organic. If anyone says their cannabis is organic, then they are not familiar with the workings of the organic program.

Established in 2004, Clean Green Certified is an independent industry organization that certifies cannabis cultivators that use natural or organic methods to grow cannabis and control pests. Chris Van Hook is a cannabis compliance and organic industry attorney and founder and director of Clean Green, a USDA National Organic Program–accredited organic certification company, of which there are only 84 globally. The Clean Green program certifies cannabis flower and products based on the federal USDA program. Not only are the flowers and products inspected by trained agricultural inspectors, but Clean Green also conducts yearly collection and testing of the soil that the plants are grown in. Soil samples are sent to a federally licensed agricultural laboratory, where they are screened for 75 indicator compounds, including synthetic pesticides, fungicides, and other prohibited synthetic compounds.

The Clean Green program tests every certified grower every year in order to renew their certification. In addition to testing for pesticides and other prohibited synthetic inputs, a general agricultural inspection is conducted of the growing and handling conditions of the certified crops. Field conditions, including dust control, are inspected, as well as are the postharvest-drying and processing areas and procedures. The goal is to ensure that proper crop production and handling standards are maintained at farms.

Once a certified crop has left a farm, a separate certification process follows the crop to the processor. This certification currently includes the making of processed cannabis products, such as pre-rolls, oils, tinctures, body-care products, and cannabis-infused food products (commonly called edibles). This certification follows the products through to the final retail packaging of the Clean Green Certified products and to the retail outlet. In this manner, similar to the USDA National Organic Program, the cannabis consumer can be confident when selecting a processed product or packaged flower with the Clean Green logo that there has been a qualified, nonconflicted, third-party certification of that purchase from seed to the

final patient or consumer.

Clean Green Certified inspectors who are either USDA inspectors or are qualified to be USDA inspectors conduct inspections on-site. Clean Green also evaluates producers and processors for fair labor and fair-trade practices, their carbon-footprint-reduction program, sustainability, water conservation, and legal water sources. Only cannabis businesses that can show compliance with their state laws may apply for a Clean Green Certification. In 2017, Clean Green certified approximately 60,000 pounds of cannabis in California, Oregon, Washington, Montana, Colorado, and Nevada. Anything certifiable under the national organic program is certifiable under the Clean Green program.

The framework that already exists for soil type, cutting solution, and pest-control mechanisms that are allowed under the national organic program is allowed in Clean Green. Again, because there are no registered pesticides for cannabis, to be legally compliant with federal pesticide laws a cannabis producer may only use products deemed so nontoxic that they do not need a federal registration for their use.

If a dispensary claims that their products are organic, then they are either not being truthful or they may think that “pesticide-free” means “organic.” If they state that their products are Clean Green certified, it is important to ask to see the certificate number for either the cultivator or producer. You can then verify the claim by going to www.cleangreencert.com.

SUMMARY

You should assume that any cannabis flower acquired in the community will be significantly contaminated with mold, bacteria, and possibly pesticides. Tinctures, vape oils, and cartridges filled with oils will probably be made with the use of butane or propane, and there is a good chance those solvents are present in the oil.

I often hear complaints that dispensary medicine is so much more expensive when compared to what you pay for cannabis sold in the neighborhood. That may be true. The states that regulate the cultivators and processors hold them to a higher standard to produce a healthy product. It is expensive to control for climate, humidity, infection, and light and to pay for state-of-the-art cultivation centers, supercritical carbon dioxide extractors, sophisticated extraction machines, laboratory testing, chemists, plant biologists, and seed-to-sale tracking. Like most things, you get what you pay for. The illegal cannabis producer is not in business for

your health, and any shortcuts to cut costs and prevent loss will be taken, regardless of whether it is in the best interest of the consumer.

When purchasing cannabis, even from a dispensary, it is advised to only purchase products that have been tested by a reputable, accredited, state-licensed, third-party laboratory. This is especially important for a patient in an immune-compromised state due to chemotherapy, AIDS, or any other condition. In some areas, the patient can take their product to licensed laboratories for testing.

In both California and Oregon, there have even been problems with community-acquired as well as dispensary-issued medical cannabis. California, until 2018, did not require testing at a statewide level, although some counties required it. Unfortunately, even where testing was mandated, without state government oversight, several laboratories were found to be falsifying results to suit the needs of the growers and processors. Not only were they falsifying the reports of THC concentrations in the products, but they were also falsely reporting lower concentrations of pesticides and other contaminants on the plants and in the extracts and concentrates.

Always ask if products have been tested by an accredited, licensed, third-party lab, and make note of the laboratory that does the testing. It is not safe to use any cannabis product—flower, oil, or concentrate—that has not been tested. Laboratory testing is not mandated in every state, and not all laboratories give honest results. If you live in a state that does not require testing or if you are purchasing cannabis in the community, be wary because labels can be deceiving! If you have an immunodeficiency, avoid inhalation, and try to use alcohol-based tinctures or cooked product.

Chapter 5

Clinical Conditions

Cannabis use has changed drastically over the years, and as our scientific understanding of cannabis expands, we are better able to reap the medical benefits from the plant without having to experience the euphoric high many adult users enjoy. When people try community-acquired marijuana for the high, they often realize there are other benefits, such as reduced pain or relief from stress and anxiety. Knowing that cannabis works best when delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are used together and with a better understanding of dosing, patients can experience its many benefits while avoiding the mind-altering and anxiety-provoking effects. Also, because cannabis no longer has to be inhaled, any adverse effects, like exposure to the carcinogenic products of combustion and irritation of the throat and lungs, are eliminated.

You might be wondering about the specific medical conditions that typically improve with cannabis therapy. You'll probably be surprised by the wide-ranging beneficial effects. Like any medication, a patient usually tries cannabis as advised by their health-care provider, and their response is monitored to determine if the desired results are achieved. Sometimes it works right away, and sometimes the dosage needs to be adjusted. There are also occasions where the medication may not address the issue adequately and needs to be changed. With guidance from a medical professional, each patient determines what is right for them.

I learn new things every day in my practice, and I'm always looking for new studies to keep up with this quickly evolving area of medicine. I have learned that cannabis can alleviate bothersome symptoms and improve quality of life for many patients, but there are a few that it just doesn't seem to help.

The endocannabinoid system's main function is to create homeostasis, or balance, and to allow the body to slow down, relax, eat, sleep, and forget. And because cannabinoid receptors are found in just about every organ

system in the human body, there are many conditions that it can target. This chapter covers some of the most common conditions for which patients seek out cannabis treatment. Also included is information about the studies that have helped to support these uses. A double-blind study means that neither the patients nor the researchers know who is receiving real medicine and who is receiving placebo, which helps to prevent bias.

The medical conditions addressed in this chapter are broken down into five basic areas: physical pain, chronic conditions, neurodegenerative disorders, mental health, and other benefits and special considerations. Physical pain is a condition almost everyone has experienced at some point. The symptoms caused by chronic conditions like neurodegenerative disease, inflammatory bowel disease (IBD), sleep disorders, autistic spectrum disorder, and even skin conditions are often alleviated with cannabis use. Cannabis has also been used by patients to successfully manage anxiety, mood disorders, schizophrenia, and post-traumatic stress disorder (PTSD). Cannabis can also be recommended for its antioxidant benefits and neuroprotective effects.

PHYSICAL PAIN

We all know what it's like to be in pain, and there are times when we will do almost anything just to make it stop. Pain can range from something minor to a debilitating condition. Medical caregivers now routinely ask patients to rate their pain on a scale of one to ten to get a general idea of its intensity. Some of us are more sensitive to pain than others, so it really comes down to how it affects you specifically. You're the only one who can tell if a treatment is effective. Managing pain allows patients to continue their lives without the distraction and inconvenience that pain causes.

Chronic pain is an enormous public health problem; approximately 85 percent of American adults will experience it at some time in their lives. Medically defined as pain lasting longer than 12 weeks, chronic pain is maladaptive; it far outlasts the precipitating injury. It affects every aspect of the patient's life—relationships, work, and school, among other things—and effectively diminishes the quality of life for not only the patient but also for the patient's loved ones. The monetary cost to society is enormous, as well. In terms of lost productivity and cost of medical treatment, chronic pain cost an estimated $500–$635 billion in 2010.[1]

In 2007, California studied the top 10 diagnoses patients were seeking to

treat with medical cannabis. All 10 involved pain and accounted for 40 percent of all diagnoses. When diagnoses were again looked at in 2011, chronic pain syndromes accounted for 80.2 percent of the conditions for which physicians wrote recommendations, with back and neck pain accounting for 30.6 percent of the conditions.[2] In my practice of cannabis medicine, approximately 36 percent of patients seen are seeking an alternative approach to alleviating chronic pain.

One in five patients with noncancer pain are prescribed opioids for pain control. In 2006, for every 100 people, physicians wrote 72.4 opioid prescriptions. That number continued to climb until 2012. In 2016, the number of opioid prescriptions written per 100 people was 66.5, still an enormous number of people taking opioid pain medication.[3] Adverse effects are common. In my practice, sedation and constipation are the most prevalent side effects, and opioid-induced hyperalgesia, in my opinion, is the most ironic.

In 2014, in the United States, two million people, or about a quarter of the patients who received prescriptions, were either abusing or dependent on opiates. Oftentimes, opiate medications were passed on to relatives or friends who already had an addiction problem. Methadone, oxycodone, and hydrocodone were the drugs most commonly involved in opiate overdoses.[4]

At present, there is an alarming increase in the number of prescription opiate overdose deaths—except in the states that have legalized medical cannabis, where the rate has decreased by almost 25 percent.[5] In 2015, there were 52,404 drug overdose deaths in the United States. Prescribed or illicit opioids were involved in 63.1 percent of those deaths. The highest opioid prescription rates were in Alabama, Arkansas, Tennessee, Mississippi, and Louisiana, while the states with the lowest opioid prescription rates were Minnesota, California, Hawaii, New York, and the District of Columbia. None of the highest opioid prescription states had medical cannabis available to their residents at the time of the survey. Since that time, Arkansas has legalized medical cannabis. All of the states with the lowest opioid prescription rates have medical cannabis programs in place.

In 2016, there were almost 1,500 deaths in Maryland due to opiate overdose, a 62 percent increase from 2015. In the spring of 2017, Maryland's governor, Larry Hogan, declared a state of emergency because of the opiate epidemic.[6]

With the pathophysiology of persistent pain, we commonly find one or more of these processes involved:

- **Nociception:** Nociceptors (nerves that respond to tissue damage from injury, temperature, pressure, and chemicals) produce a signal that travels along a chain of nerve fibers to the spinal cord and on to the brain.[7] Nociception is necessary for survival and alerts an organism that there is a problem. Other sources of pain are considered maladaptive because they continue to cause pain long after the injury is healed.
- **Neuropathy:** Damaged nerves, commonly caused by diabetes, vitamin deficiencies, chemotherapy, radiation therapy, or injury, send signals to the brain that are interpreted as pain.
- **Central Sensitization:** The brain takes what should be a relatively small pain signal and amplifies it, so that the signal is exaggerated; this can be caused by the prolonged use of opioids.[8]
- **Inflammation:** When pro-inflammatory mediators are released from damaged tissue or when a part or component of the body is mistaken for a foreign object, the immune system attacks with an influx of white blood cells and neurotransmitters that cause pain fibers to send signals to the brain.[9]
- **Emotional/Psychic:** Such states as anxiety and depression can signal the release of pro-inflammatory mediators that contribute to persistent pain.[10]

Our conventional approach to treating chronic pain includes a laundry list of pharmaceuticals. When an injury occurs, the medical provider assesses the cause and severity of the patient's discomfort and makes a recommendation for conservative treatment (ice/heat/rest); medication; and, if indicated, an exercise program or physical therapy. If the pain is not severe, usually acetaminophen or a nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen is recommended. If the pain is extreme, then an opiate and muscle relaxant might be prescribed.

If these steps do not provide relief and the pain becomes chronic (lasting longer than 12 weeks), then different medications and other treatment modalities, such as chiropractic manipulation, therapeutic massage, and acupuncture, are added to address the problems. The longer the pain remains, the longer the medication list becomes. We may then move on to serotonin-norepinephrine reuptake inhibitors (SNRIs) to relieve depression

brought on by chronic discomfort; benzodiazepines for anxiety, pain, and sleep; hypnotics for sleep; calcium-channel alpha-2-delta ligands, like Lyrica and gabapentin, for neuropathic pain; topical anesthetics and patches, such as lidocaine or diclofenac cream; tricyclic antidepressants for depression and neuropathic pain (which are effective in only a minority of patients); and anticonvulsants for neuropathic pain.

When the pain persists, we are faced with long-term use and increasing doses of medications and opiates, which increase the incidence of adverse effects like gastritis, constipation, and addiction. At this stage, patients are often on a short-acting opiate, a long-acting opiate, and another opiate (like methadone) to treat the pain that is not relieved by other opiates. Medication after medication is piled on with little effect; now the patient suffering, not only from the pain, but also from all the adverse effects of the medications!

The patient may continue to suffer from pain, despite the fact that the actual tissue has healed; for some patients, the brain has become highly reactive to almost everything—even touch—and interprets every sensation as pain. Meanwhile, the continued use of opiates actually increases the patient's sensitivity to pain via a phenomenon called opiate-induced hyperalgesia.[11] And now the patient is continuous cycle of pain.

A patient's persistent pain usually has some element of inflammation and is often accompanied by muscle spasm, neuropathy, depression, anxiety, and insomnia. In addition, there is now constipation, sleepiness, and abdominal pain from prolonged use of NSAIDs; irritability; and reduced productivity. While a condition may be categorized as inflammatory or neuropathic or mechanical, there is almost always some overlap; more than one single mechanism often contributes to the pain, which is why so many patients with chronic pain have to take more than one medication for pain relief.

Most of my chronic pain patients come in with a medication list that consists of a nonsteroidal anti-inflammatory, which they might alternate with acetaminophen, an antidepressant, a benzodiazepine for anxiety and enhanced pain relief, a muscle relaxer, an anticonvulsant for neuropathy, an opioid, another opioid for breakthrough pain, a sleep medicine, a stool softener or laxative, and a proton pump inhibitor for gastritis and reflux (see textbox 5.1). Not only do patients become depressed because of chronically not feeling well, but depression and anxiety also signal the release of neurotransmitters that increase inflammation; thus these two

emotions can actually cause physical pain. Another vicious cycle is that chronic pain interrupts sleep, which further enhances pain.

Textbox 5.1 Typical Medication List (Precannabis)

- Oxycodone: 30 mg every 6 hours as needed (pain)
- Methadone: 10 mg every 12 hours as needed (breakthrough pain)
- Ibuprofen: 800 mg every 4–6 hours as needed (inflammatory pain)
- Gabapentin: 300 mg 2 times daily (neuropathic pain)
- Alprazolam: 0.5 mg at bedtime (pain, anxiety)
- Cyclobenzaprine: 10 mg 2 times daily (muscle spasm)
- Amitriptyline: 25 mg 3 times daily (neuropathic pain, depression)
- Pantoprazole: 40 mg every day (gastritis from NSAIDs)
- Zolpidem: 10 mg at bedtime (insomnia)
- Ducolax (laxative)

There are several reasons I recommend cannabis for the relief of chronic pain. Not only does cannabis have anti-inflammatory, muscle-relaxing, and pain-relieving properties, but it also elevates mood, reduces anxiety, promotes restful sleep, and is able to potentiate the pain-relieving effects of opiates without increasing the risk of respiratory depression. Patients can achieve the same, if not better, pain relief using cannabis and a lower opiate dose.[12] Lowering the opiate dose translates into increased safety and decreased adverse effects, like nausea, sedation, and constipation.[13]

For example, a patient takes 30 milligrams of an opiate to decrease the level of lower-back pain from 8 out of 10 to 4 out of 100. When cannabis is added to the regimen, the patient is then able to lower the pain level just as much (and sometimes even further, down to 2 of 10, for example) with just 15 milligrams of the opiate, half the dose she was taking before. In fact, I find that many patients are able to decrease the opiate dose by as much as 60 to 75 percent. Furthermore, cannabis alleviates both the dull, aching, inflammatory pain *and* the sharp, stabbing, burning neuropathic pain caused by nerve damage. With the added benefit of muscle relaxation, mood elevation, and decreased anxiety, the patient feels better.[14]

Cannabis alleviates chronic pain through a variety of mechanisms.[15] It activates presynaptic CB1 receptors to inhibit glutamate and Gamma-Aminobutyric Acid (GABA) release, and modulates pro-inflammatory cytokines like prostaglandins (PGE), interleukins (IL), tumor necrotic

factor (TNF), which decreases inflammation. In conditions where there is pressure on the nerve from a bulging disc or nerves are damaged from poorly controlled diabetes, cannabis protects the nerves from further damage. Cannabis also has the unique ability to distract patients from their pain, so that even if it doesn't eliminate the pain completely, the patient just isn't as bothered by it and is better able to focus on other things. When patients respond to cannabis, it is often possible for some, if not all, of the medications to be discontinued (see textbox 5.2).

Textbox 5.2 Typical Medication List (with Cannabis)

- ~~Oxycodone: 30 mg every 6 hours as needed (pain)~~
- ~~Methadone: 10 mg every 12 hours as needed (breakthrough pain)~~
- ~~Ibuprofen: 800 mg every 4–6 hours as needed (inflammatory pain)~~
- ~~Gabapentin: 300 mg 2 times daily (neuropathic pain)~~
- ~~Alprazolam: 0.5 mg at bedtime (pain, anxiety)~~
- ~~Cyclobenzaprine: 10 mg 2 times daily (muscle spasm)~~
- ~~Amitriptyline: 25 mg 3 times daily (neuropathic pain, depression)~~
- ~~Pantoprazole: 40 mg every day (gastritis from NSAIDs)~~
- ~~Zolpidem: 10 mg at bedtime (insomnia)~~
- ~~Ducolax (laxative)~~
- Medical Cannabis:

1. **Tincture:** 1:1 CBD–THC tincture or sublingual tablet 2.5–10 mg twice daily for relief from neuropathic and inflammatory pain and to decrease anxiety, elevate mood, and relax muscle spasticity, without mental impairment
2. **Topical Cannabis Salve:** applied to area in thin layers as often as needed
3. **THC-Rich Myrcene Flower or Vape Concentrate:** 1–2 puffs followed by 1–2.5 mg of tincture sublingually (under the tongue) at bedtime for pain control and uninterrupted sleep or tincture sublingually 1–2.5 mg 30 minutes before bedtime (some patients may require higher doses)

It is difficult to categorize pain syndromes as having one source or another because of overlap between inflammation, neuropathy, and mechanical or pressure. Within each pain category, there are elements of another pain category. And while each of the following conditions are not

discussed individually, the same mechanisms that cause the pain and the same approaches to alleviating that pain apply. Some common causes of chronic pain are:

- **Inflammatory:** arthritis, gout, Lyme disease, osteoarthritis, plantar fasciitis, post-traumatic arthritis, psoriatic arthritis, and rheumatoid arthritis
- **Chronic Pain Syndromes (Neuropathic and Inflammatory):** central sensitization, cervical stenosis, complex regional pain syndrome, degenerative disc disease, fibromyalgia, low back pain, migraines, opioid-induced hyperalgesia, peripheral centralization, and reflex sympathetic dystrophy
- **Cancer-Related Pain (Mechanical, Inflammatory, and Neuropathic)**
- **Neuropathic:** AIDS-related neuropathy, allodynia, chemotherapy-induced neuropathy, diabetic neuropathy, herpetic neuralgia, phantom limb pain, radiation-induced neuropathy, and trigeminal neuralgia
- **Overuse/Mechanical:** bursitis, myofascial pain syndrome, and tendonitis
- **Connective Tissue Disease:** Ehlers-Danlos syndrome, mixed connective tissue disorder, polymyositis, systemic lupus erythematosis, and systemic sclerosis
- **Hypoperfusion (Decreased Blood Flow to Tissue):** peripheral vascular disease and sickle-cell disease

Some of the more common conditions for which patients seek cannabis therapy are related to inflammatory pain. It can be osteoarthritis from aging or post-traumatic arthritis from an old injury or surgery or psoriatic or rheumatoid arthritis, an autoimmune illness. Patients may experience inflammatory pain from a somewhat recent injury or from overuse, which leads to conditions like bursitis or tendonitis. Both CBD and THC are anti-inflammatory and pain relieving, so it is important to start with a balanced strain. I usually recommend starting with a low dose of a 1:1 ratio of CBD and THC in a tincture or tablet that dissolves under the tongue. A 1:1 ratio means that, regardless of the quantity of the two cannabinoids, they are present in nearly equal amounts. If terpene information is available, ask for strains that are high in limonene and/or beta-caryophyllene. These seem to be preferred by many of my patients.

I like sublingual administration because it is easy to figure out the right dose, and the effects last longer than inhalation. Some patients are

sensitive to cannabis's effect and might experience relief with a lower dose. A good starting dose is around 2.5 milligrams of each cannabinoid, but keep in mind that some patients respond to even lower doses. With sublingual administration, I recommend reassessing about every 20 minutes and increasing the dose if needed by 2.5 milligrams. Again, it is fine to increase with smaller doses. The point is that, wherever you start, give your body time to feel the effects of the dose before adding more. Eventually you will notice the relief. Just add up the number of drops or milligrams you took to calculate your dose (to keep track of what you are taking and how you are responding, keep a medication journal or install the Releaf App on your phone). The next time you need to medicate, you will know how much to take.

The dispensary staff will also have an idea of which strains chronic pain patients commonly use. Adjustments can always be made later if more CBD is needed for neuropathic pain or more THC is needed for more pain distraction, but this is an excellent place to start. As an added bonus, both of these cannabinoids have muscle-relaxing properties. Often, when there is pain, the brain interprets the signal as an injury and tightens surrounding muscles to stabilize the area so that you don't move and make things worse. In chronic pain, the injury is usually healed, and muscle spasms make the situation worse. Taking cannabis is like taking a muscle relaxer, a pain reliever, and an anti-inflammatory all rolled into one, which is especially helpful for patients with conditions like neck and lower-back pain.

It is unlikely to experience any high from this ratio. For a patient who has never used cannabis, they may feel uplifted or their vision or sense of smell might sharpen and colors may seem more vivid. This usually goes away within an hour or so. But because there can be laboratory errors, I advise patients to always start a new product, even if it's a 1:1, on days when they don't have to work or drive.

Patients often find relief from topical salves, especially for arthritic pain in the joints of the arms and legs. Most patients also find relief from topical products applied to their knees, ankles, shoulders, or any joint that is inflamed or painful (see textbox 5.3). The salve is applied in small amounts as often as needed. Topical cannabis only penetrates the uppermost layers of the skin, which is rich in receptors. Products with THC will not penetrate deep enough to enter the bloodstream, so there is no need to worry about psychoactivity. The only exception is if the salve is

applied to broken skin. In those instances, it is possible that THC might get into the bloodstream.

Textbox 5.3 Delores

Delores, age 62, suffered from chronic right-knee pain for two years. Her pain started when she tore her meniscus. She was initially treated with potent anti-inflammatory medications like Naprosyn and then meloxicam and piroxicam. After a year of continued pain, she had surgery to clean up the edge of her meniscus and to remove her fat pad. After surgery, the pain was not better, and she continued to have constant pain for another year. The pain and swelling made it difficult to sleep or to alternate feet when climbing or descending stairs. After several months, she also developed intermittent, sudden, sharp, stabbing pain. Delores had tried cannabis in college and found that it made her paranoid. She was working and did not want to be impaired mentally, so I recommended that she try a CBD:THC tincture with a 1:1 ratio and a topical salve. On follow-up, Delores reported that her pain had resolved in a matter of days and that she had been essentially pain free for several months. She was able to resume her old activities and was now sleeping through the night.

While not available in all medical cannabis areas, CBDA is an anti-inflammatory that differs somewhat from CBD. I advise patients to try CBDA or CBD:CBDA products when available, as well. For patients living in states that grow hemp or are approved for high-CBD/low-THC medications, there are companies that sell CBD:CBDA products in some health food stores and online. As with any nutraceutical, do your homework and make sure you are dealing with a reputable company that sells healthy products that are accurately labeled and without pesticides and other contaminants (see chapter 4).

Postoperative/Acute Pain

While there is much discussion and several studies addressing the effectiveness of cannabis in reducing chronic and neuropathic pain, little is said about its effect on acute pain. Part of the reason is that studies don't always show objective data to support the patient's subjective relief when the actual measurement of pain is done.[16] That being said, I have several patients who have chosen to use cannabis in lieu of or in combination with opiate therapy postoperatively. One female patient had shoulder surgery

and used no opiates for pain control. Another patient, aged 74, who had no prior experience with cannabis, had surgery to repair an ankle with two partially healed fractures and shredded ligaments. She took Percocet for the first few days. Hoping to avoid the constipation caused by the opioid, she titrated her dose and then managed her pain with a CBD:THC ratio of 1:1, with 10 milligrams of each cannabinoid per dose, two to three times per day. Over the course of several days, she only required Percocet for two to three doses.

Migraines (Inflammation/Neuropathy/Muscle Spasm/Anxiety/Stress)

Cannabis helps both to prevent the occurrence of migraines and to treat the pain once a migraine headache occurs. Migraine pain was once thought to be vascular in nature, but research has shown that the pain stems from inflammation of the meninges (the plastic wrap that covers the brain) and from abnormal firing of the trigeminal nerve, which causes blood vessels to dilate. CBD and delta-9 THC address both of these precipitating mechanisms. They are potent anti-inflammatories and are effective in reducing neuropathic pain. Patients also benefit from their muscle-relaxing effect and the pain-distracting action of delta-9 THC (see textbox 5.4).

Textbox 5.4 Jackson

Jackson is a 40-year-old man with a history of migraines since he was 18. He had been treated in the past with Imitrex and Botox, with no real improvement in his condition. When I first saw him a year ago, he was averaging several migraine headaches per month that would last one to two days. The severity of the headaches and concomitant photosensitivity would keep him in bed, in a quiet, dark room, for the entire day or longer. He would typically treat the pain with a prescribed opioid medication. Several times per year, Jackson's migraine pain would be so severe that it would require a trip to the emergency department.

Jackson started CBD oil, taking a small dose twice daily. When he returned for a follow-up visit, he was happy to report that, since starting CBD, his migraines had decreased in frequency to one every two or three months. The severity of the pain had decreased such that he had not needed to use any opiate medication, nor had he had any visits to the emergency department.

Clinical Trials

In addition to an abundance of anecdotal evidence and preclinical studies, there are several randomized clinical trials that have demonstrated the efficacy of cannabis in treating pain.[17]

Pain and Sleep

A small, randomized, crossover trial in Canada in 2010 showed that 25 milligrams of inhaled delta-9 THC three times daily for five days reduced pain, improved sleep, and was well tolerated.

Neuropathic Pain

A phase II, double-blind, placebo-controlled, crossover trial looking at the analgesic effect of smoked cannabis in HIV-associated distal sensory predominant polyneuropathy showed that 46 percent of subjects achieved at least 30 percent pain relief with cannabis over placebo.

Diabetic Peripheral Neuropathy

A small, short-term, placebo-controlled trial of inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain.

Sickle-Cell Pain

Sickle-cell disease is the most common inherited blood disorder in the United States, affecting about 75,000 African and Hispanic Americans. Pain can start in infancy and progresses in severity to levels that often require hospitalization. Prolonged opiate therapy is common and can lead to addiction, tolerance, and increased pain. In animal studies, cannabis has been found to mitigate neurogenic inflammation and hyperalgesia (increased sensitivity to pain) in mice with sickle-cell disease. The study, conducted at the University of Minnesota, demonstrated that synthetic cannabinoids were effective in reducing pain; potentially protected organs from hypoxia or reperfusion injury, oxidative stress, and inflammation; and possibly slowed the progression of the disease.[18] The research group was granted a 9.5 million dollar grant from NIH to conduct clinical trials on human patients, using a 1:1 CBD:THC ratio of vaporized cannabis provided by National Institute on Drug Abuse. The study was moved to the University of California at San Francisco in conjunction with Donald Abrams. This trial is still in progress.

Cancer-Related Pain

A 2010 multicenter, double-blind, randomized, placebo-controlled British study of 170 cancer patients with pain inadequately controlled by opiates examined the efficacy of cannabis. Patients were divided into three groups and received extracts with CBD:delta-9 THC, delta-9 THC, or placebo. The results showed a statistically significant decline in pain scores in the CBD:THC group. Compared to the placebo group, twice as many patients in the CBD:THC group (43 percent) experienced a reduction of more than 30 percent from baseline.

In summary, both CBD and delta-9 THC are effective in relieving nociceptive, inflammatory, and neuropathic pain. Both distract from pain and address the commonly occurring comorbidities (other medical conditions) that contribute to chronic pain—anxiety, depression, muscle spasm, and insomnia. Research indicates that when CBD and delta-9 THC are combined, the medicine is more effective at reducing pain than with either cannabinoid alone.[19]

CHRONIC CONDITIONS

Autistic Spectrum Disorder

Autism is characterized by varying degrees of deficits in communication and social skills, as well as by stereotypic behaviors, restricted areas of interest, and abnormal sensory issues. Autistic symptoms affect one in 68 children in the United States, with severity ranging from moderate social anxiety and awkwardness to profound social isolation, impaired verbal expression, sleep disturbances, and heightened neurosensory sensitivity.[20] Patients with autism often display anxiety-driven behaviors, varying degrees of shyness, inability to understand and respond appropriately to social cues, and extreme difficulty adjusting to changes in routines or transitioning from one activity to another.

As children with autism age and grow in size and strength, temper tantrums that were once only inconvenient become increasingly difficult to manage. When frustrated or angry, anxiety and poor impulse control can lead to physical attacks on and aggression toward teachers and parents. To compound the problem, many of the antipsychotic medications used to treat their symptoms of aggression and rage slow metabolism, so these patients often gain a tremendous amount of weight (see textbox 5.5).

Textbox 5.5 Timothy

Timothy is a 13-year-old boy who was diagnosed with autism when he was two years old. He has limited verbal skills and other behaviors stereotypical of autism. Over the years, there were no significant behavior issues until he began going through puberty. Once small and somewhat timid, Timothy was now taller than his mother and weighed more than 160 pounds.

He was fine as long as he had his way, but if he did not get what he wanted, he would have violent outbursts—physically assaulting teachers and his mother. He was treated by his neuropsychiatrist with a number of medications, including sertraline, clonazepam, risperidone, and aripiprazole, without success; the latter two medications compounded the problem by contributing to substantial weight gain.

Timothy was started on a CBD-dominant formulation with less than 0.3 percent THC that did not have to be held under the tongue but was swallowed. This CBD product is emulsified, so it is more water soluble for better gastrointestinal absorption. As always, the parents were asked not to advise the school so that we could get feedback on his behavior without the placebo effect of knowing that he was on a new medication.

By the fourth day of therapy, parents and teachers both noticed a marked improvement in behavior. At the six-month follow-up visit, Timothy was reported to be calmer, sleeping better, and doing much better at handling frustration and anxiety without hitting.

Approximately 30 percent of patients with autism also have a seizure disorder.[21] Anecdotal reports from parents who have used cannabis to treat their children's seizures indicate that the use of cannabis not only helps control their seizures but also mitigates the aggressive behavior, helps with sleep, and in some cases improves expressive language and social interaction. It's important to remember that cannabis can improve or impair social interaction in a dose-dependent manner.[22]

Recent research implicates altered endocannabinoid signaling and neuroinflammation as possible contributors to autistic behaviors.[23] When mice who are genetically programed for fragile X syndrome, a condition commonly associated with autistic behavior, were treated with a compound to increase circulating levels of 2-AG, a naturally occurring endocannabinoid that our bodies make when needed, researchers observed a dramatic improvement in behavior in maze tests that measure anxiety

and comfort levels in open spaces (mice naturally prefer crevices and small spaces where they can hide).[24]

A 2010 Austrian case study chronicled the behavioral improvements in a six-year-old child with autism who was treated with dronabinol, a synthetic THC, the same molecule as found in the plant and that attaches to the same receptors. The child was on no other medication and showed statistically significant improvement in irritability, lethargy, stereotypic behavior, hyperactivity, and inappropriate speech.[25]

The pediatric neurology department of Shaare Zedek Medical Center in Jerusalem is conducting a large crossover, double-blind, placebo-controlled study of CBD treatment in 120 individuals with mild to severe autism. It is expected that the study will continue through 2018.

Autoimmune Disease

Autoimmune diseases include Addison's disease, celiac disease, chronic fatigue syndrome, fibromyalgia, Graves' disease, Hashimoto's disease, Lyme disease, mast-cell disorders, mixed connective tissue disease, myasthenia gravis, psoriasis, scleroderma, Sjogren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis. These conditions happen when the body's immune system mistakes its structures for foreign objects and attacks. This can cause a myriad of symptoms, depending on which organ systems are involved.

Regardless of the diagnosis, there are several symptoms that may be alleviated with cannabis use. Symptoms that occur in most autoimmune diseases include headache, fatigue, muscle pain, joint pain and swelling, poor appetite, impaired memory or concentration (brain fog), nausea, diarrhea, bloating, and abdominal pain. Both THC and CBD are potent anti-inflammatories, pain relievers, and muscle relaxants. CBD has been shown in preclinical studies to regulate the autoimmune system by decreasing substances produced by the body that cause inflammation (see textbox 5.6).

Textbox 5.6 Adam

Adam was diagnosed with psoriatic arthritis and colitis at age 14. The chronic inflammation caused pain in his joints, gastrointestinal inflammation, abdominal pain, and diarrhea. Unrelated to his inflammatory illness, Adam also suffered from Asperger's syndrome, a mild form of autism commonly associated with high levels of anxiety,

especially in social situations. In addition to sulfasalazine, medication to treat his autoimmune disease, Adam was taking multiple medications to alleviate his anxiety.

At the time of his first appointment, his antianxiety regimen included aripiprazole (Abilify) which commonly causes excessive weight gain. At that time, Adam suffered with arthritic flare-ups in his knees several times a year. He had gained 30 pounds from taking aripiprazole and was still having bouts of severe abdominal cramping and bloody diarrhea.

We decided to start Adam on a combination of CBD and CBDA. He experienced a modest amount of relief, and as we increased his dose, his arthritic and colitis symptoms improved somewhat. We tried to lower his aripiprazole, but this caused his anxiety to increase. We added THCA, another nonintoxicating cannabinoid found in the raw plant, in small amounts. Adam continued to improve. After one year, he was no longer having painful arthritic or colitis flare-ups, he was no longer missing days of school, and he was able to hold down a part-time job. Eventually he was able to discontinue aripiprazole, and the medicine he was taking to control his colitis (sulfasalazine) was lowered to one-fourth the dose he was taking before starting cannabis. At 18 months after the start of treatment, Adam was able to discontinue all but two medications for anxiety, his inflammatory markers were down, and he was no longer having painful flare-ups.

The efficacy of cannabis in the treatment of pain and gastrointestinal symptoms has been well documented in preclinical trials and by anecdotal evidence. Less understood are the effects of cannabis on symptoms like chronic fatigue and brain fog. Many patients find that cannabis, at low to moderate doses, increases their energy level and their ability to focus. When pain is persistent, THC distracts the patient’s attention away from their pain and thus improves function and quality of life. With autoimmune illnesses, CBD is recommended for its anti-inflammatory and autoimmune regulatory effects. I generally suggest starting with 20 milligrams of CBD twice a day and titrate up until there is improvement in symptoms. If needed, I recommend using THC for pain distraction or mood elevation, starting with 2.5 milligrams twice a day. Most of my patients are not interested in being intoxicated or stoned, and as long as there is more CBD onboard than THC, there is usually not a problem. If needed, the THC can be increased until it is equal with the CBD in a 1:1 ratio, but most of these

patients don’t need that much THC. Studies have shown that THC at 20 milligrams is relatively ineffective at treating pain, so I don’t recommend patients taking more than 15 milligrams. For nighttime comfort and sleep, a dose of one to five milligrams of THC at bedtime is usually enough.

Myasthenia gravis is an autoimmune disease that causes weakness and fatigue of the skeletal muscles. With myasthenia gravis, the body makes antibodies that attack certain proteins in the muscles, most commonly acetylcholine receptors, but there are others that can be involved. These receptors are necessary for the muscles to be able to contract when they get a signal from the brain to do so. When the receptors are not available, the nerves are unable to transmit their signals to the muscles. This muscle weakness can cause double vision, droopy eyelids, difficulty swallowing, generalized weakness, and fatigue. Patients are usually able to recover during the night, so they often have more energy in the early part of the day, but they get progressively weaker and more fatigued as the day progresses. Cannabis modulates the autoimmune system by decreasing the inflammatory mediators that are causing the problem. Many patients experience increased energy and ability for their muscles to respond to the signals the brain is sending. There is quite a bit of anecdotal reports of patients with myasthenia gravis responding to CBD-rich, CBD:THC, and THCA products (see textbox 5.7).

Textbox 5.7 Nancy

When Nancy came to my office for the first time in April 2017, she had been in a wheelchair for two years. In December 2016, six months before her first visit, this retired critical-care nurse had been hospitalized, intubated, and placed on a ventilator because of an upper-respiratory and blood infection. Her muscles were too weak to allow her to breathe adequately. The severity of her myasthenia gravis, which was diagnosed 11 years prior, was such that Nancy would have to decide each day whether to bathe because the energy she exerted in doing so would exhaust her so that she would not be able to do anything else for the rest of the day. She had so much difficulty swallowing that she was fed pureed food through a feeding tube placed in her stomach to prevent aspirating food particles into her lungs. The double vision she experienced from weak eye muscles prevented her from reading. Having a conversation for more than a few minutes was difficult. Her voice would just fade away after a short period of time. A sluggish gastrointestinal tract (gastroparesis) and poor

gastroesophageal sphincter tone caused chronic nausea and vomiting, which led to several episodes of aspiration pneumonia.

Nancy was also treated for diabetes mellitus, a consequence of chronic steroid treatments, with both long- and short-acting insulin; to further complicate her condition, she suffered from chronic and severe neck pain due to a nondisplaced cervical fracture and herniated disc. Her medication list also included medication for hypertension, pantoprazole (proton pump inhibitor for gastritis), steroids, and Lyrica. Opioids had been discontinued because of fear of exacerbating her gastroparesis and causing respiratory depression.

At her first visit, I recommended CBD oil, starting at a low dose to modulate her autoimmune system, and dronabinol, a synthetic delta-9 THC, for chronic pain, nausea, and vomiting. Nancy increased her dose slowly, as instructed, but did not experience much change in her strength or fatigue. Later that summer, she and a friend traveled to Amsterdam, where she consulted with a physician familiar with cannabis. She was instructed to increase her CBD dose, which she did. Within a week, her double vision had resolved so that she was now able to read. Her swallowing also improved significantly, so she was able to eat regular food.

When Nancy came for her follow-up appointment three months after returning from Amsterdam, she walked into the office using a cane. Nancy was no longer wheelchair bound. She was able to eat popcorn and other foods that she had not been able to manage for years. Her blood sugars were no longer elevated, and she was no longer taking insulin. At a more recent follow-up, Nancy was happy to announce that her feeding tube had been removed and her steroids and pyridostigmine (to treat myasthenia gravis) had been discontinued. She was now able to go out for dinner and to the theater with her friends, and her quality of life had improved exponentially.

Cancer

Cannabis has long been known to alleviate many of the unpleasant symptoms associated with cancer treatment, such as nausea and vomiting. It can also stimulate appetite, relieve pain, increase energy, reduce anxiety, elevate mood, and promote restful and restorative sleep. Many patients who have had to undergo several rounds of chemotherapy marvel at how

much better they felt when they used cannabis during their treatment—with or without psychoactivity. For some patients, the high that comes with THC, with its mentally relaxing and amnestic effects, can be a welcome respite from the worries of confronting a chronic or life-threatening illness. Here it is especially important to start with a low dose and gradually increase by small increments until the desired effects are realized. What is also remarkable about the plant is its ability to decrease and sometimes prevent chemotherapy- and radiation-induced neuropathy. In addition, many anecdotal cases have reported prolonged length of life and, in some patients, eradication of the disease.

Cancer is characterized by uncontrolled cellular growth and its ability to invade other tissues. This unregulated growth is the result of mutations caused by damaged DNA, cell-cycle defects, and inadequate apoptosis. Cells mutate all the time. What differentiates a person who develops cancer from one who does not is the ability of the patient's immune system to eliminate potentially malignant cells before they have time to grow, invade, and metastasize.

Cells in the body die because of either necrosis or apoptosis Necrosis occurs from external damage—toxins, lack of blood supply, or infection. Cellular death by necrosis causes inflammation that can precipitate further damage to the body, thus some of the complications associated with chemo and radiation. Apoptosis is referred to as cellular suicide. It is a programmable, organized cellular death that occurs within the body and nucleus of the cell. It is cleaner than necrosis and lacks all the pro-inflammatory cellular debris caused by necrosis. When there is insufficient apoptosis, mutant cells are left unchecked and continue to grow into malignant, invasive tumors.

While there are approximately 400 compounds in the cannabis plant and close to 150 cannabinoids, the cannabinoids most studied for possible cancer treatment are CBD, THC, CBDA, and THCA, but others have also been used in animal and test tube studies. These compounds contribute to the plant's ability to target malignant cells by increasing apoptosis, causing them to self-destruct. There are also potent antioxidants and anti-inflammatories, which may add to their antitumor effects.[26]

As early as the 1970s, animal studies found that cannabinoids increase apoptosis and inhibit tumor growth in lymphomas; breast cancer; prostate cancer; certain brain tumors, like gliomas and neuroblastomas; and certain lung, liver, skin, and pancreatic malignancies. A 2016 South African study

showed a significant increase in apoptosis with an isolated CBD extract in four types of cervical cancer.[27] CBD, the major nonpsychoactive cannabinoid, not only inhibits tumor growth by increasing apoptosis, but it also impedes metastasis by interfering with cell migration and adhesion. In addition, it can interrupt the tumor's ability to create blood vessels. Without a blood supply, the tumor is unable to feed itself and can't grow.[28] Israeli studies have shown that there is more to know about what's in the plant besides the THC and CBD content. Test-tube studies have shown that other cannabinoids, like THCA and CBDA, influence how a particular strain of cannabis affects some cancer cell lines, where THC and CBD do not.

Animal Studies

There are hundreds of in vitro and animal studies showing the effects of cannabis on certain tumors. Unfortunately, not everything that occurs in the laboratory translates predictably to man. We don't know exactly which phytocannabinoids, their amounts, and their combinations are needed to eliminate certain cancers or why it can eradicate cancer in some patients and not others. The following findings from some of these studies done on mice were published in 2015 review[29:29]

- **Gliomas:** Microdoses of THC and CBD reduced tumor size in several cell lines. The effect was greater than with THC or CBD alone. THC and temozolamide (chemotherapeutic) reduced tumor size greater than THC or temozolamide alone.[30]
- **Colon Cancer:** CBD, across different cell lines, reduced the number of polyps and tumors, tumor growth, and metastasis.[31]
- **Liver Cancer:** THC decreased ascites. Anandamide reduced tumor growth.
- **Pancreatic Cancer:** THC reduced tumor growth. Synthetic THC (WIN55) reduced growth and spread.[32]
- **Breast Cancer:** CBD decreased tumor growth and metastasis. THC increased tumor growth and metastasis.[33]
- **Prostate Cancer:** CBD in similar doses in one cell line decreased tumor growth and in a different cell line increased growth.[34]
- **Lung Cancer:** CBD reduced tumor size in various cell lines. THC reduced tumor size in one cell line but had no effect on another.[35]
- **Thyroid Cancer:** Synthetic cannabinoids VDM-11, AA-5-HT, and met-

AEA reduced tumor size.

- **Melanomas:** THC reduced tumor growth.[36]
- **Cervical Cancer:** CBD rather than cannabis crude extracts halted proliferation in all cell lines.[37]

Despite the abundance of evidence that the endocannabinoid system is an understudied frontier in developing treatments for cancer, cannabis therapy for cancer has not been adequately studied in humans because it is a Schedule I substance and is deemed to have no medical benefit by the DEA.

Cannabinoids obviously do not reduce or eradicate cancer cells in every patient and should not be sought out as the only means of treating cancer, especially if the cancer is considered curable by conventional therapy. Over the years, I have evaluated a handful of patients with tumors with very high cure rates by conventional therapy who forego surgery, chemotherapy, or radiation in favor of cannabis therapy. This is a huge misinterpretation of the evidence available. I advise patients to not depend on cannabis as a cure for cancer. It is, however, a safe, natural, and effective way of alleviating nausea and vomiting, preventing and treating chemo-induced and radiation-induced neuropathy, stimulating the appetite, promoting restful and restorative sleep, and alleviating anxiety and depression. It can also relieve pain or potentiate the pain-relieving effects of opiates so that patients are more comfortable, more alert, and less constipated, all leading to an improved quality of life.[38] Whatever contribution it makes to the reduction or elimination of malignant cells and tumors is an added bonus (see textbox 5.8).

Textbox 5.8 Janet

When Janet, age 61, decided to try cannabis, she had already undergone extensive treatment for lung cancer. Part of her upper-left lobe had been removed, and she had an inoperable mass in her right lung, for which there was no further treatment. She also suffered from chronic arthritic joint pain. I recommended that Janet start taking 50 milligrams of CBD twice a day to alleviate her joint pain; hopefully, it would also slow down the progression of her cancer. A year later, Janet is cancer free.

We have no dosing guidelines for treatments. Every patient has to find the dose that works for them. I recommend a very low-dose oil made from

as many as ten different varieties of cannabis so that the patient gets the maximum variety of terpenes and flavonoids working with the cannabinoids. And because we don't know which cannabinoids are effective in eradicating which cancer cell lines, I usually recommend that patients use a cannabis oil that has both acidic and neutral forms—THCA, CBDA, THC, and CBD in equal parts so that each dose is 0.5 to 1.0 milligrams, four times daily. If it is not available in the dispensary, patients or family members may have to make it themselves. Some cancer lines respond to very small doses of cannabinoids, whereas others respond to high doses. Patients are encouraged to continue care with their oncologist, and over time, if there is not response, I suggest increasing the dose. Usually, patients are taking larger doses of THC and CBD to help alleviate nausea and vomiting and to hopefully prevent chemotherapy- or radiation-induced neuropathy.

Dermatology: Treating the Skin

The skin is rich with cannabinoid receptors, and the anti-inflammatory and antioxidant effects of cannabis make it an effective topical for conditions like eczema, psoriasis, and acne.[39] Patients using cannabis for other reasons often report that their psoriatic plaques or eczema have improved or gone away completely.

Historically, cannabis leaf powder has been used to relieve pain and itch. Hemp seed oil has been used to treat eczema, psoriasis, lichen planus, seborrhea, and rosacea. Cannabis salves are effective at relieving the itch and inflammation associated with mosquito and other insect bites and has been found to prevent post-inflammatory hyperpigmentation. Both THC and CBD exert their anti-inflammatory effects by activating receptors in the first two layers of the skin. They do not penetrate the deeper layers or bloodstream unless formulated on a transdermal patch.

Glaucoma

Despite the fact that glaucoma is on the list of qualifying conditions in many medical cannabis states, it is a condition that is difficult to treat with cannabis, especially inhaled cannabis, which is generally effective for only two to three hours. It is THC, and not CBD, that lowers intraocular pressure. CBD is neuroprotective and may be beneficial by protecting the optic nerve and retina from the damaging effects of increased pressure.

I recommend cannabis as an adjunct treatment for glaucoma and stress to

my patients that it is imperative that they continue to use the drops prescribed by their ophthalmologists.

Clinical Endocannabinoid Deficiency

In 2003, Ethan B. Russo wrote a paper postulating that abnormal endocannabinoid function might play a role in the pathophysiology of migraines, fibromyalgia, irritable bowel syndrome, and other difficult-to-treat conditions that lack a clear-cut etiology but are responsive to cannabis therapy.[40] For many years, clinicians didn't know what to do about some of these syndromes. Because we did not understand the pathophysiology of these conditions, many of us unfairly lumped patients with symptoms that could not be explained, substantiated, or alleviated by conventional treatments into what was sometimes referred to as functional problems. The under-the-surface implication was that the symptoms might be anxiety driven or attention seeking. The endocannabinoid system is not taught in medical school, does a great disservice, not only to the patients, but also to the young doctors who will soon be faced with trying to help these patients heal and feel better. Now we find that abnormal endocannabinoid signaling just may play a role, not only in fibromyalgia and irritable bowel syndrome, but also in autism, chronic pain syndromes, seizure disorders, and a host of other conditions, including aging.[41]

Endocannabinoid Overactivity

The endocannabinoid system modulates appetite, fat metabolism, insulin sensitivity, and glucose metabolism. It is postulated that an overactive endocannabinoid system can lead to increased appetite, somnolence, and metabolic syndrome (obesity, diabetes mellitus, hypertension, and hyperlipidemia).[42]Animal and human studies bear this out. One study showed that inactivating the CB1 receptors decreased appetite, body fat, and plasma lipids in normal and obese mice, but activating CB1 receptors increased weight and triglyceride levels.[43] A 2009 human study evaluated 49 overweight men with increased intra-abdominal fat. Anandamide, 2-AG, HDL-cholesterol, and triglyceride levels were measured, and tests for insulin sensitivity and glucose tolerance were performed. The subjects were subjected to lifestyle changes that included a healthy diet and exercise for one year. At follow-up, the subjects had lost statistically significant amounts of weight. Decreases in waist circumference, intra-abdominal fat, 2-AG levels, anandamide, and serum triglycerides and an

increase in HDL cholesterol were also statistically significant. While there was a decrease in anandamide levels, it was not as profound as the decrease in 2-AG. Further analysis of the data suggested that it was the decrease in intra-abdominal fat and 2-AG, and not anandamide, that correlated with the improvement in triglyceride and HDL cholesterol levels.[44] To date, endocannabinoid hyperactivity continues to be an area of interest and research.

Infectious Diseases

Hepatitis C

Hepatitis C has become an increasing problem in American baby boomers —people born between 1945 and 1965. The reason for this outbreak is not entirely understood. While cannabis does not cure hepatitis C, the symptoms of nausea and fatigue that patients often experience are alleviated with cannabis therapy. When interferon is used to treat hepatitis C, the side effects of the medication often are so severe that it is difficult for patients to complete the full treatment regimen.[45] Cannabis has been found to safely alleviate those symptoms enough so that patients can complete their treatments. With the newer direct-acting antiviral treatments now available, severe adverse effects are not as common because the medications are better tolerated.

HIV and AIDS

Cannabis does not suppress the immune system and is not known to be detrimental to the immune status of patients with AIDS. To the contrary, patients with HIV or AIDS benefit from cannabis therapy in a number of ways. It stimulates the appetite, alleviates nausea and vomiting,[46] alleviates neuropathic pain, reduces anxiety, elevates mood, and promotes restful and restorative sleep. Cannabis use should be spaced two hours from antiretroviral therapy because it has the potential to interfere with the metabolism of certain drugs in this classification.

Antimicrobial Effects

In the nineteenth and twentieth centuries, cannabis was used to treat parasitic infections like malaria. We now know that there are several cannabinoids and terpenes that have antibacterial, antiviral, and antifungal effects. In a 2008 study, THC, CBN, CBD, CBG, and CBC were found to

be highly effective against a number of methicillin-resistant staphylococcus aureus (MRSA) strains.[47] Further research is being done to see how we can use these compounds to fight this difficult-to-treat infection.

Conditions of the Gastrointestinal Tract

Inflammatory Bowel Disease

Abdominal pain, weight loss, diarrhea, and fatigue are typical symptoms for patients with Crohn's disease and ulcerative colitis and can be alleviated with cannabis therapy. The gastrointestinal (GI) tract is rich with cannabinoid receptors. The endocannabinoid system is known to decrease intestinal motility, inhibit the production of inflammatory cytokines, induce apoptosis, improve epithelial wound healing, decrease intestinal permeability, reduce gastric acid secretion, and reduce visceral pain.[48] THC binds directly to the cannabinoid receptors in the GI tract, and CBD increases the levels of anandamide, a naturally occurring cannabinoid. They are especially effective at reducing gastric and intestinal inflammation.[49] Both THC and CBD alleviate abdominal pain, and it appears that CBD regulates GI motility that, when out of balance, causes either diarrhea or constipation. It has also been found in preclinical studies to protect the cells that line the gastrointestinal tract. Cannabinoids also inhibit the disordered intestinal permeability during inflammation and often help symptoms associated with the immunoglobulin G (IgG) inflammatory response caused by unhealthy bacterial flora in the intestines or food sensitivities, which can lead to leaky gut syndrome.[50] Leaky gut is thought to lead to inflammation throughout the body and cause conditions like chronic fatigue, joint pain, and autoimmune illnesses.

A 2013 randomized study published in *Clinical Gastroenterology and Hepatology* showed that an eight-week course of THC-rich cannabis produced significant benefits to 90 percent of patients with active Crohn's disease compared to placebo.[51] It is important for inflammatory bowel patients to remember that an improvement in symptoms does not always correlate with the healing of ulcerations or remission, and it is imperative to continue monitoring your condition with your gastroenterologist.

Arthritic joint pain can be an extraintestinal manifestation of IBD. It and intestinal inflammation caused by autoimmune illnesses like psoriatic arthritis may also respond to courses of cannabis therapy. CBD capsules

seem to be more effective than other forms. With THC's mood-elevating effects and CBD's energizing and antianxiety effects, patients often feel better as their intestinal tracts heal. Patients with Crohn's disease and ulcerative colitis often report that their appetite improves, they have more energy, and they experience fewer flare-ups (see textbox 5.9).

Textbox 5.9 Linda

When Linda came to my office the first time in 2016, she was pale, thin, and sad. Her 33-year battle with Crohn's disease was wearing her down. In the past few months, she had been suffering with abdominal cramps, diarrhea, and poor appetite, and her weight had gone from 115 pounds down to 98 pounds.

Linda was treated aggressively with immunosuppressive drugs, including Entyvio, Humira, and Remeron. She suffered intolerable adverse effects from almost all of them. She experienced severe muscle tightness from Humira and muscle weakness from Remeron. While on Entyvio, Linda had repeated bouts of difficult-to-treat urinary tract infections.

Her colonoscopies always showed severe inflammation and fistulas. Linda had undergone four surgeries to remove parts of her intestines. In 2012, approximately one foot of bowel was removed and an ileostomy was performed. With this procedure, an end of the bowel is brought to an opening made in the abdominal wall and attached. A bag is attached to collect fecal output. When it was time to reconnect the ends of the intestine, Linda was still so symptomatic that she opted to keep the ostomy, but she continued to have abdominal cramping and diarrhea.

We started a CBD/CBDA oil in 2016 and gradually increased the dose over several weeks until her symptoms began to improve. It took about one month before her appetite increased, the cramping stopped, and the diarrhea slowed down. Linda began to increase her activities and gain weight.

I saw Linda for follow-up about three months ago, and she was thrilled to inform me that her most recent colonoscopy was completely normal—the first normal result in more than 30 years! Her gastroenterologist told her to keep doing what she was doing, and we will!

Irritable Bowel Syndrome

Severe abdominal pain, bloating, and diarrhea or constipation characterize the symptoms commonly associated with irritable bowel syndrome.[52]

Endocannabinoid signaling is altered in these patients compared to patients without symptoms. IBS is also thought to be one of the conditions explained by clinical endocannabinoid deficiency (CED). Many patients are treated with varying degrees of success with antiemetic (antinausea) and antispasmodic medication. Many experience relief with dietary changes—eliminating fermentable sugars (FODMAPS, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols). Others find no relief or find it very difficult to follow the elimination plan.

There is no inflammatory component in IBS, and symptoms are often exacerbated by stress or anxiety. Cannabis, especially CBD, relieves anxiety, interrupts the hypothalamic-pituitary-adrenal stress response, reduces visceral pain, and regulates gut motility. THC does not seem to be as effective, so I usually recommend a CBD:THC ratio of 20–30:1. I have followed several patients with diarrhea that slows down or resolves with the use of CBD. Many patients who suffer from chronic or intermittent constipation find that, with cannabis use, bowel movements become softer and more regular.

Gastroesophageal Reflux Disease (GERD) and Esophagitis

CBD decreases gastric acidity, but at high doses it may also delay gastric emptying and decrease the tone of the sphincter that keeps stomach contents from sliding up into the esophagus, which in theory could exacerbate GERD symptoms.[53] There is now evidence that GERD is a function of inflammation, not increased stomach acid; NSAIDs irritate the stomach lining, and many of these patients have gastric symptoms for that reason.

In my practice, most patients with GERD and esophagitis experience an improvement in their symptoms. The benefits of CBD on gastric inflammation may outweigh the other issues. Patients using cannabis to treat other symptoms may also be able to reduce or eliminate NSAIDs and other medications that cause gastric irritation and inflammation.

I did have a young, nonverbal patient with autism and a history of prematurity and significant gastroesophageal reflux since birth. His parents had started him on rather high doses of CBD in hopes of improving his expressive language. On the days they gave it to him, he would cry and flap his hands anxiously. The oil seemed to be causing him distress. I advised his parents to discontinue CBD. On follow-up the irritable behavior had resolved. It was my thought that the CBD might have been

causing more discomfort associated with reflux because of the effect on sphincter tone.

Acholasia (Esophageal Spasm)

Cannabis can be effective in alleviating severe spasms of the esophagus that cause pain, weight loss, and difficulty sleeping. Early in my cannabis medicine practice, I saw a patient with this condition who had been on multiple medications and had undergone several major surgeries, called myotomies, to cut the esophageal muscles so that food could pass. Despite this aggressive approach, he continued to have difficulty eating. Food would sometimes get stuck, and he suffered from extreme discomfort from spasms that made it nearly impossible to sleep through the night.

He started with a couple of drops of a hemp-derived oil that had both CBD and CBDA and less than 0.3 percent of THC. The patient reported that, within a few days, food was no longer being caught in his esophagus, he was able to eat more, and he was sleeping through the entire night for the first time in eight years.

Intractable Hiccups

Hiccups are caused by spasm of the diaphragm. They are called intractable when they persist for 30 days or longer. They are often treated with anticonvulsant or antipsychotic medication, both of which can have significant side effects. I have treated a few patients with CBD, which has been effective in reducing the frequency of the hiccups or stopping them completely.

Conditions of the Central Nervous System

Included in this section is cannabis's effect on epilepsy and seizure disorders, hypoxic ischemic brain injury, Huntington's chorea, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, Tourette's syndrome, and dystonia. One of the first case studies on childhood epilepsy, the "Case of Infantile Spasm," was written by Dr. William B. O'Shaughnessy and printed in the *Royal Medical Journal* in 1843. From then until the 1930s, cannabis was used by physicians in Europe and the United States to treat seizures.

CBD came to the forefront of public knowledge via a television special that told the story of Charlotte, who was a healthy baby until she was three months old, when she began having uncontrollable seizures. By age two, she was diagnosed with a seizure disorder called Dravet syndrome. By age

five, Charlotte was having about 300 seizures per week. At that time, she had lost her developmental milestones, was nonverbal and wheelchair bound, and received nourishment through a feeding tube inserted in her stomach. Her parents, desperate to help their child, whose condition by this time was so severe that the doctors and family had made the heart-wrenching decision to not resuscitate in the event she were to stop breathing, had read about the use of marijuana in treating seizures and decided to try it. They found a high-CBD, low-THC variety at a dispensary and, with the help of a friend, made an extract for her to take. Her improvement was almost immediate; she went several days without a seizure. In 2013, Charlotte's story was made famous by a television special, "Marijuana and Charlotte's Web," with Dr. Sanjay Gupta.[54] Since then, hundreds of thousands of children with seizures have been treated with CBD with varying degrees of success.

How CBD modulates seizure activity is not well understood. Animal studies have shown that, after a seizure, there is an increase in the levels of the endocannabinoid anandamide in the brain. It is thought that, when anandamide attaches to the receptors, it interrupts the aberrant signaling. CBD, which interferes with the enzyme that breaks down anandamide and thereby increases the anandamide levels, has been found to have significant anticonvulsant effects in mouse models.

In 2016, GW Pharmaceuticals published the results of a multicenter, double-blind, placebo-controlled, crossover study on the effectiveness of CBD in alleviating seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome. There were 120 participants in the study, who were on an average of three antiepileptic drugs (AED). The patients received Epidiolex, a purified 98 percent oil-based CBD extract, starting at a dose of five milligrams per kilogram per day in addition to their baseline AED regimen. The daily dose was gradually increased by two to five milligrams per kilogram increments at one to two intervals until intolerance occurred or they reached a maximum dose of 25 milligrams per kilogram per day. Half received Epidiolex, and half received placebo. The Epidiolex group achieved a median reduction in monthly convulsive seizures of 39 percent, compared with a reduction in the placebo group of 13 percent, which was considered highly statistically significant. A new drug application was filed with the FDA and received priority review status, which accelerates the timing of the FDA review. It is anticipated that approval may occur sometime in mid-2018.

Hypoxic Ischemic Brain Injury: Traumatic Brain Injury (TBI), Postconcussion Syndrome, and Stroke

When increased pressure from a blow to the head or an atherosclerotic plaque, shock (hypoperfusion), or a ruptured blood vessel result in insufficient blood flow, areas of the brain are deprived of oxygen, which causes tissue damage and cell death. This results in an inflammatory response and the release of free radicals (oxidative stress) and other toxic compounds that lead to neuronal death.[55]

There are a number of animal studies that have shown promise in the use of cannabinoids to decrease neuroinflammation and limit the effects of neurotoxins, such as glutamate and reactive oxygen species (ROS), that are released after an ischemic event and cause cell injury.[56] CBD has been found in these studies to reduce ischemic injury to brain cells, improve blood flow, reduce brain edema and seizures, and improve brain metabolic activity.[57] Research has found that, while THC also has these effects, its usefulness is limited by the development of tolerance. After a while, it loses its effect. That's not the case with CBD. Researchers found that repeated treatment with CBD did not lead to development of tolerance in the cerebro-protective effect to the damaged area of the brain and that CBD continued to increase cerebral blood flow (CBF) even after 14 days of repeated treatment.[58] Studies looking at clinical outcomes of patients with brain injuries found that those who tested positive for THC had statistically significant improved survival rate when compared to patients who tested negative and improved recovery when compared to patients who had never used cannabis.[59]

NEURODEGENERATIVE DISORDERS

The anti-inflammatory, antioxidant, and neuroprotective properties of cannabis can also be of benefit to patients suffering from neurodegenerative disorders.

Huntington's Disease

Huntington's disease is an autosomal-dominant inherited movement disorder characterized by choreiform (sudden, uncontrollable, writhing) movements due to loss of motor inhibition. Researchers have found that patients with Huntington's disease have abnormal endocannabinoid signaling and decreased numbers of CB1 cannabinoid receptors in the

basal ganglia, an area of the brain that is involved in controlling movement.[60] Preclinical studies show that both THC and CBD reduce neuroinflammation, oxidative stress, and edema.[61] There is also data to suggest that cannabinoids may slow the progression of the disease through their neuroprotective and anti-inflammatory mechanisms.[62]

Cannabis may not be effective in reducing the choreiform movements.[63] A 1991 randomized, double-blind, placebo-controlled, crossover study of 15 patients with Huntington's disease were treated with CBD at 10 milligrams per kilogram. The average dose was seven hundred milligrams per day for six weeks. At the end of the study, there was no significant improvement in symptoms, nor were there any adverse effects when compared to placebo.[64] Another using a 1:1 CBD:THC compound did not show significant improvement with movements when compared to placebo. However, in a small, randomized, double-blind, placebo-controlled, crossover study of 44 patients using a synthetic THC, nabilone, at one or two milligrams, there was significant improvement in total motor and chorea scores on the unified Huntington's disease rating scale. No adverse effects were reported.[65]

Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disease affecting the central nervous system and characterized by neuroinflammation and Lewy bodies, which are clumps of proteins within the cells in the brain.[66] Symptoms of the disease include tremor, stiffness, abnormally slow movements, impaired balance, and slurred speech. Some patients experience psychosis (hallucinations). Symptoms are due to the loss of neurons that produce the neurotransmitter dopamine.[67]

Although there is not much clinical data in the scientific literature to support the effectiveness of THC in decreasing the tremor, I have two patients in my practice who have responded positively to THC. Both patients have a severe tremor, which has been unresponsive to conventional therapy. One patient purchased THC-rich cannabis in the form of a 10-milligram edible, and the other was treated with the synthetic THC dronabinol at 10 milligrams twice daily. Both patients experienced a significant decrease in their tremors, with the effects lasting about three to four hours, allowing them time to shave, dress, and eat without help; they said this significantly improved their mood and quality of life. I have other patients who at the time did not have access to THC and medicated with

CBD, which had no effect on relieving the tremors.

In a 2014 double-blind study of 21 patients with Parkinson's disease treated with CBD at 300 milligrams per day, there were no statistically significant differences in the unified Parkinson's disease rating scale (UPDRS) scores; however, there was a statistically significant difference in the Parkinson's disease questionnaire scores, suggesting that CBD may improve quality of life for these patients without untoward side effects.[68] CBD has antipsychotic properties, and a small study showed that six Parkinson's patients treated with CBD showed a significant decrease in psychotic symptoms without worsening motor function.[69]

It is reasonable to try CBD for its anti-inflammatory, anxiolytic, neuroprotectant, and antipsychotic benefits. If more than 300 milligrams per day is needed, increases should be done cautiously. One study showed that exceeding that dose exacerbated the bradykinesia and resting tremor.[70] When recommending cannabis for Parkinson's disease, I have patients start with a CBD:THC ratio from 10–20:1 at 20 milligrams twice daily for daytime use. They are instructed to increase the dose gradually until they feel their symptoms are relieved. I advise taking a small dose of THC (2.5 milligrams) at bedtime. I keep the patient on this dose for about one week to give the body time to become accustomed to the effects of THC while sleeping. Doing this minimizes the risk of adverse intoxicating effects that might worsen the already-existing problems with balance and gait. I then proceed to increase the dose by 2.5 milligrams per week until the patient is ready to try a small daytime dose. We then gradually increase the dose until the patient experiences decreased tremors. When patients are only bothered by their tremors periodically during times of self-care and meals, inhalation is a good alternative for dosing THC, where the effects will only last two to three hours.

Multiple Sclerosis

Multiple sclerosis consists of a constellation of symptoms caused by changes in the myelin sheaths that coat nerve fibers and expedite the transmission of signals from the brain to the body and vice versa. Symptoms typically include sensations in arms and legs, loss of vision in one eye, double vision, difficulty walking, balance problems, dizziness, bladder problems, seizures, cognitive changes, and depression. Pain is a very common problem and can include trigeminal neuralgia; Lhermitte phenomenon, where bending the neck causes a sensation resembling an

electric shock that radiates down the spine or into the limbs; chronic migraines; and persistent neurogenic pain. Muscle spasms affect most patients with multiple sclerosis and can impair ambulation and self-care to the extent of functional disability.

Using CBD reduces anxiety, relaxes the muscles, and eases neuropathic pain. It may also slow down the progression of the disease. THC can be added to maximize muscle relaxation and pain relief. Using it with CBD during the day will mitigate the intoxicating effect. Using THC alone at bedtime will help with sleep. Cannabis salves and balms can be applied topically to relieve muscle spasticity. It's important to try different ways of delivery to find the one that works best for you.

Amyotrophic Lateral Sclerosis (ALS)

ALS, commonly known as Lou Gehrig's disease, affects nerve cells in the brain and spinal cord. Onset is typically gradual, and symptoms vary from person to person. The hallmark of the disease is progressive muscle weakness and paralysis. In addition to weakness, symptoms may include muscle spasms and emotional lability. CBD and THC together in a balanced variety reduce anxiety and elevate mood. Through its neuroprotectant and antioxidant properties, cannabis may slow down the progression of the disease in some patients.

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease characterized by progressive cognitive decline, memory loss, and behavioral changes. Amyloid plaques and neurofibrillary tangles are the hallmarks of the disease. Studies show that cannabinoid receptor are involved in the pathogenesis of Alzheimer's disease.[71] An underlying inflammatory process and oxidative stress have also been implicated as part of the pathophysiology of the disease.[72] Cannabis's anti-inflammatory and antioxidant effects may contribute to attenuating symptoms associated with the disease and slowing disease progression. It has also been shown that THC interferes with the deposition of the characteristic beta-amyloid plaques.[73] Animal studies have shown that, in areas of neuronal damage, there is an increase in the number of cannabinoid receptors and an increase in the production of endocannabinoids—perhaps nature's way of providing protection.

Timing of cannabinoid therapy may be crucial. Another animal study has

shown that augmenting the levels of endocannabinoids early in the disease process may offer some protection, but increasing cannabinoids late in the disease may exacerbate memory problems. A small 2016 Israeli study showed that 10 of 11 patients in an open-label trial treated with THC showed a statistically significant reduction in agitation, aggression, delusions, irritability, and apathy. Patients slept better, ate better, and experienced overall a better quality of life. It was also noted that their caretakers felt better as well.[74]

I recommend starting low-dose THC (1.25 milligrams) at bedtime to help patients sleep through the night, as wandering can be a problem. It may take a few nights of gradually increasing by 1.25 milligrams before seeing the results. After a week or so of bedtime dosing, a small daytime dose can be tried at mealtimes to help stimulate appetite. If psychoactivity is undesired or not tolerated, adding CBD will attenuate that effect. You have to balance the ratio so that the CBD doesn't suppress the oftentimes already-limited appetite.

Tourette Syndrome

As early as 1993, THC has been found by clinicians to be effective in reducing the number of motor tics, vocal tics, and obsessive-compulsive urges characteristic of Tourette syndrome. A Swiss case study of anecdotal reports found that, of the patients who used cannabis, 82 percent experienced a reduction or complete remission of the motor and vocal tics.[75] In another study, 12 patients were treated with THC in a single dose, resulting in improved Tourette syndrome symptom list scores and a reduction in the number of observed motor tics. A 2002 small, randomized, double-blind, crossover trial showed a significant improvement in patients who received THC when compared to placebo. It was also noted that there were no serious adverse effects. Patients usually start with 2.5 milligrams twice a day if dosing under the tongue or three to four times per day if dosing by inhalation and gradually increased dosage until the tics were extinguished.

Dystonia (Spasmodic Torticollis)

The cause of dystonia is not completely understood, but it does not appear to be neurodegenerative in nature. It seems to be more related to cellular function and may be related to the neurotransmitter dopamine, the same neurotransmitter that is depleted in Parkinson's disease. It can cause

muscle spasms and neuropathic pain.[76] Anecdotal evidence suggests that a CBD:THC ratio of 1:1 might be the best approach to relieving the muscle spasms and pain associated with this condition.

MENTAL HEALTH

Anxiety

I am often asked if cannabis is an appropriate and effective treatment for anxiety. Anxiety is actually one of the more common complaints I hear from patients who use or are considering medicinal cannabis. Oftentimes, patients suffer from social or performance anxiety that interferes with their ability to carry out certain tasks required by their job (e.g., speaking in front of a large group). This type of situation often causes shortness of breath, sweating, flight of ideas, rapid heart rate, and feeling faint—a panic attack. Or the patient experiences ongoing anxiety driven by the pressure to meet deadlines, quotas, or sales goals. This type of anxiety often leads to headaches, forgetfulness, neck pain from muscle spasm, poor appetite, chronic nausea, poor concentration, or disturbed sleep.

The antianxiety effects of certain varieties of cannabis do not always stem from THC. While low doses of THC can squelch anxiety, an exacerbation of anxiety and even paranoia can occur when strains with high levels of THC are used or if the patient uses too high a dose. CBD is the cannabinoid primarily responsible for treating anxiety and mental stress. It is thought to affect anxiety via mechanisms of action in the limbic and prelimbic areas of the brain. Unlike THC, CBD has little binding affinity for either the CB1 or CB2 cannabinoid receptors found in the brain. Instead, it interacts directly with a number of other receptors to produce a variety of therapeutic effects. One of those receptors is the 5-HT1A serotonin receptor, which helps mediate a variety of biological and neurological processes, including anxiety. By binding to the receptor, CBD slows down 5-HTIA signaling, which in turn minimizes the body's excitatory responses, thereby reducing anxiety, depression, and aggression.[77] A 2010 Brazilian double-blind, crossover study demonstrated that pretreatment with 600 milligrams of CBD mixed with corn oil and dosed in a gelatin capsule significantly reduced anxiety, cognitive impairment, discomfort, and alert levels in a simulated public-speaking test.[78]

CBD is not intoxicating, so it's an appropriate workday treatment. A few drops of tincture under the tongue will start to take effect in 20 to 30 minutes, and the effects can last 5 to 8 hours. I recommend staying with the same dose for 4 to 5 days before making any increases. Dosing sublingually with an oil or lozenge may require twice-a-day dosing. Because CBD at low doses can be alerting, some patients choose to use a higher dose at night for its sedating effect or use a THC-rich variety at night to alleviate anxiety and help with sleep.

For unexpected anxiety-provoking situations, like having to speak publicly or make a presentation, vaporized CBD takes effect within 10 minutes and is effective for 2 to 4 hours. For patients with severe anxiety and a history of panic attacks, I recommend carrying a disposable CBD vape pen for emergencies. Usually two to three puffs are adequate for aborting the attack. Most patients prefer this over using a rescue medication like alprazolam or diazepam, which can cause drowsiness.

Depression

Cannabis has been used to treat depression and melancholia for hundreds of years. THC can elevate mood, as demonstrated in numerous animal studies. CBD has been shown in preclinical studies to have antidepressant effects comparable to the antidepressant imipramine. This antidepressant action is thought to be mediated by activation of the 5-HT1A receptor, which is a subtype of serotonin receptors. These receptors are involved in the mechanism of action of many medications used to treat depression. Antidepressants, like SSRIs, increase 5-HT1A signaling.

A 2012 longitudinal study of more than 45,000 Swedish men failed to demonstrate an increased risk of depression in cannabis users.[79] Anecdotal patient reports, however, suggest that CBD can make depression worse, so for patients with depression, I usually recommend that CBD be combined with a small amount of THC. I generally recommend that the CBD:THC ration be no higher that 5:1 to 10:1, which means that there is five to ten times more CBD in the preparation than THC. Patients whom I have followed with major depressive disorder, situational depression, and postpartum depression (who are not nursing) have been relieved by using strains that are CBD dominant but have small amounts of THC.

Mood Disorder

There are no clinical studies on the therapeutic effects of cannabis on

bipolar disorder; however, there are a number of anecdotal reports of patients with bipolar disorder responding to cannabis. I have treated a number of patients either self-referred or referred by their mental-health provider with bipolar disorders types 1 and 2, as well as schizoaffective disorder, which is bipolar disorder with psychotic features.

In 1998, Lester Grinspoon, associate professor emeritus of psychiatry at Harvard Medical School, published a case series reporting mood stabilization.[80] While the exact mechanisms that cause bipolar disorder are not known, it only stands to reason that cannabinoids would help, given that they alleviate symptoms of other conditions that are typically treated by the same medications that are used for mood—antidepressants, anxiolytics, anticonvulsants, hypnotics, and antipsychotics, all with significant adverse effects. It is important to keep in mind that substance use disorder is higher in this population of patients than in the general population. Cannabis should not be used recreationally but only under medical supervision.

CBD reduces anxiety, has antidepressant and antipsychotic effects, and appears to be a mood stabilizer. Care must be taken to only use CBD-dominant varieties of cannabis because too much THC can initiate or exacerbate psychotic symptoms. I have found that patients do well using a CBD:THC ratio of 20:1 for type 1 and with a higher THC content but no higher than a 1:1 for patients with type 2.

Post-Traumatic Stress Disorder (PTSD)

PTSD is on the list of qualifying conditions for medical cannabis recommendations in several states with medical cannabis laws. PTSD is a constellation of symptoms that arise from frightening or threatening events that cause psychological trauma, such as a history of personal physical or sexual violence; experiences involving the death, life-threatening illness, or trauma of a loved one; a natural disaster or life-threatening illness or event such as a heart attack or motor vehicle accident; participation in or exposure to violence, such as combat or witnessing death or serious injury. Symptoms include flashbacks; hypervigilance or being in an alert, watchful state when there is no reason; sleep disturbance with difficulty falling asleep and staying asleep; nightmares; intrusive thoughts; and avoidance of anything that might be a reminder of the traumatic event. Patients with PTSD often suffer from other psychological problems, particularly anxiety and depression.

Memory, particularly long-term memory, is stored in a structure of the brain called the hippocampus. This structure is part of the limbic system, which is the area of the brain that regulates emotions. The hippocampus is where we remember important things like how to read, how to play a musical instrument, or how to speak a language. Not surprisingly, the effect of THC on memory occurs within the hippocampus. And while it is important to remember some things, it is equally important not to remember everything. I once had the opportunity to hear the scientist who first identified THC at a conference at Harvard Medical School. He explained that part of the endocannabinoid system's role is to prevent us from remembering the things that are not helpful or important, such as *every* face we encounter in the grocery store. After all, who needs *that*?[81] The effect of THC on memory is generally considered an adverse effect; however, in certain situations, the endocannabinoid system may be instrumental in facilitating the extinction of conditioned fear associations and responses.[82] So, while it is good to remember, there are some things that are best forgotten. THC stimulates those receptors in the brain that facilitate the extinction of painful memories.

There are a few animal studies that can serve to guide us with THC treatment in PTSD. One study looking at the effects of THC on rats exposed to a traumatic event showed that those who were treated with a synthetic THC displayed far fewer symptoms of PTSD than rats who were not treated. An earlier preclinical animal study had shown that, while cannabis did not erase the recollection of the experience, it was effective in preventing the development of PTSD if administered within twenty-four hours of the event.[83] Subsequent research suggests that it may be effective when used even later.

In addition to calming anxiety, lifting mood, and helping us forget unpleasant events, our endocannabinoid system promotes restful sleep. When a patient uses cannabis strains with THC, the amount of time spent in slow-wave sleep increases, thus decreasing the duration of rapid-eye movement (REM) sleep. It is during this phase of sleep that most of our dreaming occurs. This is helpful for PTSD patients who are plagued by nightmares and night terrors.

A 2014 Canadian study looked at the effectiveness of nabilone, a synthetic CB1 agonist, in the treatment of insomnia, nightmares, anxiety, and chronic pain in inmates with multiple mental health diagnoses, including PTSD. They found that 89.6 percent of the subjects reported

increases in sleep of at least two hours, a decrease in the frequency of nightmares, decreased anxiety, and improved functioning at levels that were all statistically significant.[84] In 2014, a retrospective study of PTSD patients in New Mexico showed 75 percent fewer overall symptoms with cannabis use.[85] A 2015 Canadian double-blind, placebo-controlled, crossover study done on military personnel with PTSD showed that nabilone was effective in relieving nightmares in patients with a history of prior treatment failure.[86]

I encourage patients with PTSD in my practice to use a CBD:THC variety with a slightly higher THC content, like a 1:2 for daytime if their symptoms are severe and they are not working. This is usually effective in eliminating any anxiety, which most of my patients also have. If working and driving, then it is best to stay with a 1:1 during the day to avoid any psychoactivity and for both insomnia and nightmares, THC in the evening and at bedtime.

Schizophrenia

On occasion, a patient who is not doing well despite numerous medication changes and adjustments will be referred from a psychiatrist. Among conditions that appear to benefit from high-CBD/low-THC cannabis therapy are schizoaffective disorder and schizophrenia.

It was once thought that cannabis caused schizophrenia. It is now known that there are a number of events that might precipitate the onset of symptoms in patients who are genetically predisposed to developing schizophrenia, and exposure to high levels of THC is one of them. That being said, cannabis-related psychosis, which is not the same as schizophrenia, is a brief dose-related reaction to THC, an adverse effect that is not associated with causing a permanent psychotic illness, though the long-term effects are not known or understood.

What surprises most people is that not only is CBD anxiolytic, but it also has antipsychotic properties and stabilizes mood. These effects are most probably mediated via 5-HT receptors that modulate anxiety, depression, and psychosis. Another cannabinoid, THCV, has also been shown in animal studies to enhance 5-HT1A receptor activation, which may explain some of its antipsychotic effects.

Interestingly, many studies looking at the effects of cannabis on schizophrenia find an association with better cognitive functioning in schizophrenic patients using cannabis than those not using cannabis. In

2009, a review was done of 23 studies on cognitive functioning and cannabis. Fourteen studies showed that cognitive functioning was better in schizophrenic patients using cannabis compared to nonusers. In eight studies, no difference between the two groups was found, and in only one study found that the group using cannabis did not function as well as the nonusing group.

Interestingly, another 2009 study, though very small, looked at the use of synthetic THC (dronabinol) in treating inpatient psychiatric patients who were resistant to antipsychotic therapy. Of the six patients treated, four showed improvement in core psychotic symptoms, not just nonspecific calming.[87] In another study, CBD compared favorably with amisulpride, an antipsychotic. Both CBD and amisulpride were found to have similar efficacy, but CBD caused far fewer side effects.[88]

It has been stated that cannabis use increases the risk of developing schizophrenia by 40 percent, and the earlier the cannabis use, the greater the risk; however, we may find that increased cannabis use may be merely an early indication of schizophrenia in patients who may be self-medicating psychotic symptoms.[89] It is completely plausible that cannabis use, and especially early cannabis use, can be a soft sign of impending or evolving mental illness.

A small study conducted at Rockland Psychiatric Hospital in New York demonstrated THC's antipsychotic effects. Six patients with psychotic symptoms who had failed to improve despite several medication changes were treated with dronabinol, a synthetic THC. They were started on a 2.5 milligram dose that was gradually increased. All but one patient improved to the extent that they were not just calmer, but also their psychotic symptoms resolved.[90]

Stress

The physiological response to stress is a chain reaction of chemical and hormonal signaling that prepares the body to fight or run. When we perceive a stressor, the hypothalamus releases neurotransmitters that signal the pituitary, which in turn stimulates adrenal glands to produce corticosteroids. It is via the hypothalamic-pituitary-adrenal (HPA) axis that we are able to react to a dangerous or threatening situation. The stress response is adaptive when it sends us into a fright-flight state necessary to survive danger. As I tell my patients, it is what was required for our caveman ancestors to escape the fangs of the saber-toothed tiger. Once the

danger is no longer a threat, it's important that we return to a state of balance because chronic stress can wreak havoc on our bodies.

This cascade of events and the increasing levels of corticosteroids causes an increase in heart rate and oxygen intake via the volume of air we breathe in and respiratory rates, or how fast we breathe. It triggers a shift in blood flow away from the digestive tract to the periphery where blood is needed to get arms swinging and legs running. Thus, we experience poor appetite, nausea, and sometimes diarrhea or constipation. Prolonged exposure to these substances leads to weight gain, elevated blood sugars, high blood pressure, increased susceptibility to infection, inability to sleep, and fatigue.

Endocannabinoid signaling is intricately involved in the regulation of the HPA axis and prevents the activation of the system during nonstressful periods. When exposed to stress, the activity of the enzyme that metabolizes anandamide, fatty acid amide hydrolase (FAAH), increases, which causes the levels of anandamide in the amygdala area of the brain to go down, allowing for activation of the system. Once the system is activated, the increased levels of glucocorticoids then act in a retrograde manner to increase anandamide levels, which then shuts down the response. In other words, a stressful situation downregulates anandamide so that you are not too relaxed to react to the situation. Then the increased levels of the stress hormones upregulate anandamide so that you can return to your relaxed state.

One of the reasons a patient might not be able to return to that relaxed state could be a glitch in the feedback to the brain that the problem has been noted and everything is under control. This failure to decrease FAAH activity keeps anandamide levels low and sustains the stress response. When the stress response is prolonged, it causes a number of physiological problems that can literally make us sick.

Many of the patients I evaluate are highly functioning but are in highly stressful professions. Others are stressed by economic conditions, familial dysfunction, or a chronic illness of themselves or a loved one. Commonly, patients experience difficulty turning off the workday tension once they are at home, or the conditions under which they live keep them in a state of hyperresponsiveness.

CBD acts by inhibiting the FAAH enzyme, thus mimicking the action the increased levels of glucocorticoids should have but didn't do—downregulating FAAH activity so that anandamide levels in the brain can

rise. Higher levels of anandamide, in turn, signal the adrenal glands, the production of glucocorticoids is interrupted, and the stress response is terminated.[91]

OTHER BENEFITS AND SPECIAL CONSIDERATIONS

Protecting the Heart, Stomach, and Brain

Cannabis is known to have neuroprotective and antioxidant properties. There are no clinical trials to verify whether using cannabis in small doses has a protective measure. Animal studies suggest that it does. In the discussion on TBI, I mentioned the mechanisms by which CBD is neuroprotective. Studies show that CBD and CBDA are gastrocytoprotective (protects the cells lining the stomach and intestines) and CBD and THC are cardioprotective.[92] In preclinical studies, mice were pretreated with CBD and then inflicted with a heart attack. The areas of ischemic damage caused by the lack of oxygen to the heart muscle was significantly smaller in the mice who had been receiving CBD.[93] THC protects cardiac cells against hypoxia via CB2 receptor activation.[94] Similar results have been obtained in experiments involving stroke. The area of damaged brain tissue was smaller in pretreated animals. Some patients choose to take a small daily dose of CBD-rich tincture or a balanced CBD:THC tincture for just those reasons. There are no formal dosing recommendations, so I recommend taking a small dose of one to two milligrams of a balanced-variety tincture four to five days per week in the morning or at bedtime.

Glucose and Fat Metabolism

CBD regulates fat and glucose metabolism. Patients with diabetes mellitus who find it difficult to control their blood-sugar levels often find that, after they begin taking cannabis for other problems, their blood-sugar levels come down! It may be that emotional issues that drive overeating are relieved so that the need to eat for comfort is also alleviated and that CBD decreases appetite. CBD is a partial CB1 antagonist and may also be responsible for dampening CB1 activity in an overactive endocannabinoid system. A 2012 study found that cannabis users had smaller waistlines, and fasting-insulin levels were 16 percent lower than in subjects who did not use cannabis.[95]

Insomnia and Sleep Apnea

Restful sleep is crucial to good health. Poor sleep negatively affects quality of life and performance. People with inadequate sleep suffer from fatigue, anxiety, depression, excessive daytime sleepiness, and confusion at a higher rate than people who are well rested. Aging can also lead to sleep disturbances because, as people age, the amount of time spent in slow-wave sleep decreases. Anxiety, depression, and obstructive sleep apnea can lead to sleep fragmentation, where patients wake up repeatedly during the night.

Slow-wave sleep, or stage 3 sleep, in particular, is a deep, restorative sleep that is necessary for the body to recharge and regenerate. Inhaled cannabis increases the amount of time a person is in slow-wave, non-REM sleep, thus increasing the quality of sleep. Patients awaken feeling energized and refreshed. According to a small study published by the University of Illinois Department of Medicine, THC in doses of 2.5 to 10 milligrams taken daily stabilized autonomic output during sleep, reduced spontaneous sleep-disordered breathing, and blocked serotonin-induced exacerbation of sleep apnea. Many patients who use cannabis to help with sleep do so without the typical addiction or withdrawal symptoms associated with conventional hypnotics.

Intimacy

Sometimes referred to as nature’s Viagra, cannabis has been known to enhance sexual pleasure for thousands of years. In traditional Ayurveda medicine, cannabis is listed as a drug that improves male sexual function by delaying ejaculation.[96] In a survey of self-reported responses in 23,000 men and 28,000 women, cannabis users had a statistically significant higher frequency of sexual intercourse than subjects who had never used cannabis.[97]

Both THC and CBD are anxiolytic, meaning they relieve anxiety, and relax muscles. Cannabis upregulates oxytocin, the hormone involved with human interaction, sometimes called the bonding hormone, and oxytocin levels are increased during orgasm and breastfeeding. It also relieves pain, and elevated levels during labor keep mothers from experiencing even higher pain levels than they do. Oxytocin modulates the initiation and expression of maternal behavior in mammals and in humans enhances the ability to evaluate other people’s facial expressions for both obvious and hidden emotions.[98]

Cannabis is known anecdotally to not only facilitate reaching female orgasm but also to potentiate or strengthen orgasm. Many couples find that using cannabis with sex decreases anxiety, relaxes the muscles in the body, and alleviates the pain that might otherwise interfere with sexual pleasure. The effect of THC on memory helps some patients let go and take their minds off of pressing matters or worries that sometimes get in the way of enjoying sex to the fullest. For women with decreased vaginal lubrication as a consequence of menopause or medication, topical vaginal lubricants are available. Patients who have experienced a decrease in libido because of medication for depression sometimes find that using a balanced strain of cannabis with THC and CBD elevates their mood enough to lower the dose of those medications or eliminate their need, which helps reduce side effects. For some patients, THC's effect on sense of time makes it seem like their sexual responses are going on and on. It also enhances tactile perception and induces a euphoric state. Patients must keep in mind that cannabis has a biphasic effect, and taking too much THC may actually interfere with sexual pleasure. It's important to be mindful of how much cannabis you use and start with small doses, gradually increasing until you experience the effect you are looking for.

Harm Reduction and Withdrawal

Several studies have shown that, when cannabis is used, more often than not, the intake of other substances like alcohol and opiates, and even cigarettes, goes down. People who are going to abuse drugs will abuse drugs, and they tend to start with the drugs that are most accessible. Those are usually tobacco, alcohol, and marijuana. Studies have failed to show that using marijuana in of itself leads to use of more harmful drugs. The National Institute of Drug Abuse has removed references to cannabis as a gateway drug from their website.

No one thinks to himself, "When I grow up, I want to be a drug addict." Life's circumstances and mental health issues may lead some people to using illicit, highly addictive drugs. Many are victims of the medical community's overzealous effort to make patients pain-free with prolonged opiate therapy. Generally, the bottom line is that many of these people who use drugs, prescribed or not, just want to feel better than they are feeling. Cannabis not only alleviates many of the symptoms for which patients receive addictive prescriptions, but it also alleviates many of the symptoms that lead some people to self-medicate.

While some drug use is strictly recreational or a consequence of boredom coupled with poor judgment, depression, anxiety, psychosis, mood disorder, physical pain, and PTSD are often underlying conditions that lead to the use of alcohol, cocaine, methamphetamines, benzodiazepines, opiates, and hypnotics. When cannabis is used, many patients find that the need for these other substances decreases because, not only do they feel better, but also cannabis helps mitigate some of the withdrawal symptoms they would experience otherwise. I have evaluated countless patients whose alcohol and tobacco consumption has decreased significantly, and without much effort, after starting cannabis therapy (see textbox 5.10).

Textbox 5.10 Jason

Jason is a 68-year-old man who was referred to me by one of his specialists. He had a long history of anxiety, depression, and Crohn's disease, which caused severe abdominal pain and diarrhea. Jason also suffered from chronic arthritic and neuropathic pain in his knees and feet.

He was being treated with an antidepressant (gabapentin), an anti-inflammatory (prednisone), an immunosuppressive biologic (adalimumab), and antianxiety medication. Jason reeked of tobacco and admitted to smoking approximately 40 cigarettes per day for several years.

The Maryland dispensaries were not yet open, so to start, I recommended a 20:1 CBD:THC oil for him to take during the day to alleviate his anxiety and gastrointestinal pain, to regulate his gut motility, and to relieve his chronic inflammatory and neuropathic pain in his knees and feet. I also advised Jason that the tobacco smoking was adding to his inflammation and pain and that he should make every effort to stop smoking.

When Jason returned for a follow-up visit one month later, his abdominal pain and diarrhea had resolved; his anxiety and lower extremity pain had improved; and without much difficulty on his part, his tobacco smoking had decreased from 40 cigarettes to 10 cigarettes per day.

Special Considerations in Pediatrics

The American Academy of Pediatrics (AAP) has weighed in on the cannabis controversy. While it is opposed to legalization for fear of increased use in adolescents (which has not panned out in states with legalized cannabis), it now acknowledges that some patients may actually benefit from cannabis medicine and supports the rescheduling of cannabis

by the DEA so that further research can be done. The AAP also recommends the following:

- Research and development should be conducted of pharmaceutical cannabinoids. The AAP recommends changing marijuana from a DEA Schedule I to a DEA Schedule II to facilitate this research.
- The federal and state governments should establish robust health surveillance regarding the impact of marijuana, particularly on children and adolescents.
- In states that have legalized marijuana for recreational use, the AAP strongly recommends strict enforcement of rules and regulations that limit access, marketing, and advertising to youth.
- Where marijuana is sold legally, either for medicinal or recreational purposes, it should be contained in child-proof packaging to prevent accidental ingestion.
- The AAP discourages adults from using marijuana in the presence of children because of the influence of role modeling by adults on child and adolescent behavior.

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's symptoms and improve their quality of life, and does this benefit outweigh any possible risk of adverse effects that can be attributed to this treatment? If the answer to these two questions is yes, then I make the recommendation.[99]

The majority of children I see are self-referred, meaning their parents have read that cannabis might help their symptoms and they are desperate to ease their children's suffering. They are sometimes rebuffed by their pediatrician or specialty care provider, so they decide to find another provider to help them. Others are referred by either pediatric primary care physicians or pediatric specialists, such as neurologists and gastroenterologists.

The majority of pediatric patients I evaluate have a seizure diagnosis. The next most-common diagnosis is autism and chronic and debilitating pain. Most of the pediatric seizure patients have many seizures a day, some upward of 100. These patients typically are diagnosed with infantile spasms, Dravet syndrome, or Lennox-Gastaut syndrome. Aggressive behavior and anxiety associated with autism is another common complaint. As children grow, they become heavier and stronger and can hurt teachers

and family members. Pediatric patients also present with such conditions as Crohn's disease, ulcerative colitis, Ehlers-Danlos syndrome, Lyme disease, and mitochondrial disorders. In all diagnostic categories, adverse effects from pharmaceuticals can also be the driving force.

Pediatric patients are typically started with CBD because it is often effective, is not known to have any effects of neurodevelopment, and is not intoxicating. CBD can be energizing at low doses and sedating at high doses. Higher doses can also be associated with diarrhea and increased salivation. Parents should not give low doses of CBD too close to bedtime, and for children who require higher doses, care has to be taken so they are not sleepy in school. CBD's suppressive effect on appetite means that special care must be taken with picky eaters with already small appetites, so growth parameters must be carefully monitored.

Dosing can be tricky. Cannabis is neither FDA approved nor regulated, and it is often difficult for patients to receive dosing at school or in daycare. Because they are usually on some type of antiseizure medication whose metabolism might be altered by dosing CBD too closely, it sometimes requires special planning and adjustments in schedules so that there can be a 1.5- to 2-hour space between dosing those medications and CBD.

Children are usually dosed with tinctures. When they are able to cooperate with sublingual doses, I generally recommend that mode of delivery. An alternative can be placing the drops between the cheek and lower gum, where some oromucosal absorption is possible before the child is able to swallow the medicine (medicine is absorbed directly into the bloodstream through the small capillaries in the mouth). New micro- and nanoemulsion technology makes it possible to dose some children who will swallow the medicine right away or who protest to the extent that it needs to be hidden in food or drink.

When CBD is not effective, I generally go to low-dose THCA for seizure control, anxiety-driven behavior issues, and pain relief. I have found it to be often well tolerated and effective in all three conditions. Many parents will use low-dose THC as a rescue medication for status epilepticus (seizures lasting more than five minutes). It is often preferred over diazepam and other typical medications because it does not leave the child so sedated. I have also recommended microdoses of THC for anxiety-driven aggressive behavior in children and young adults with autism.

Parents in nonmedical states have access to hemp-derived CBD online.

The industry is not FDA regulated, and there are unscrupulous merchants who sell oils that have no CBD or concentrations much lower than advertised; some oils are loaded with pesticides, mold, solvents, and or heavy metals. That being said, there are other companies that make a quality product that is safe and consistent.

Parents should find physicians in their area with knowledge of the CBD market, who can guide them toward safe products. There are only two states that have no laws allowing for cannabinoid medicine: Kansas and Idaho. Parents in those states have to carefully weigh the pros and cons and exercise extreme caution should they choose to administer CBD to their children because it is still technically a Schedule I substance and, without state legislation, could result in reports to child protective services by a school, friend, health-care provider, or relative.

In November 2017, the World Health Organization reported that no adverse health outcomes had been identified with CBD and that it should not be scheduled as an internationally controlled substance. The Expert Committee on Drug Dependence (ECDD) begins an expanded review of CBD in May 2018. Hopefully, at that time, more specific recommendations will be made and lead to legalization at the federal level.

An excellent review in the *Journal of Pediatric Pharmacology* sums up how cannabis is currently being used in the pediatric population for epilepsy and behavioral issues associated with autism. It also highlights its potential use in decreasing neural damage caused by birth trauma and in treating neuroblastoma, a childhood malignancy that usually occurs in the adrenal gland. The article also raises concerns regarding adolescent use and increases in unintentional ingestions by children.[100]

Special Considerations in Geriatrics

Geriatrics is defined as medical care for patients who are 65 years old or older. Approximately 36 percent of my patients are 50 and over, and many have very complicated medical histories and are on a laundry list of medications. The majority of patients in this age group present with chronic pain, neurodegenerative disease, and autoimmune disease.[101]

Most of my geriatric patients experience significant relief with CBD-rich or balanced varieties of cannabis. While some appreciate the mental alterations imparted by THC-rich strains, most are not particularly interested in getting high. Care must be taken in geriatrics because they tend to be more sensitive to the adverse effects of delta-9 THC.

Cardiovascular Concerns

Acute use of THC can cause an increase in heart rate and blood pressure, which can be problematic for patients with uncontrolled atrial fibrillation or other forms of tachycardia. Chronic or long-term use of THC can lower blood pressure and heart rate, so patients with bradycardia, or abnormally low heart rates, or low systolic blood pressures (under 100) might suffer from decreased blood flow to the heart if the pressure or heart rate dropped too much. Patients with cardiac instability, poor ejection fractions, severe congestive heart failure, or at high risk of myocardial infarction (heart attack) should exercise extreme caution with cannabis. When I first started to evaluate California patients via telemedicine, there were a few who I absolutely would not have approved had it not been for the fact that they had been using cannabis already and for a long time. One of these patients with chronic pain and significant heart disease had an ejection fraction of 28 percent (normal is greater than 55 percent).

Acute use of cannabis can cause an increase in heart rate and blood pressure in some patients. This could pose a problem for geriatric patients with uncontrolled hypertension or with a condition like atrial fibrillation, where the heart is beating at a rate that is too fast. I have treated many patients with hypertension or atrial fibrillation that is well controlled with medication or who have undergone a procedure called cardiac ablation without incident. Patients with either of these conditions are often on a medication called a beta-blocker. Atenolol, propranolol, and metopralol are all metabolized by cytochrome p450 enzyme 3A4, the enzyme used by CBD and THC. Particularly when a patient is using CBD, it is important to dose it two hours from these medications. Likewise, patients with irregular or rapid heart rhythms are often treated with medication like warfarin (Coumadin) to prevent blood clots. This medication, too, requires 3A4 for proper metabolism and clearance and should be dosed two hours from CBD.

Chronic use of cannabis can cause decreases in systolic pressure in some, but not all, patients. This can be a benefit for patients with hypertension but can increase the risk of dizziness or syncope (fainting), with either situation exacerbating a patient’s risk of falling. The cerebellum is the area of the brain that controls coordination, and it is rich with CB1 receptors. THC, which activates CB1 receptors, can cause problems with coordination and balance, another potential increase in the patient’s risk of falling. High doses of THC can also affect memory and orientation, which

can add to already-existing memory problems or problems with confusion or disorientation. Last, older patients tend to be more vulnerable to the anxiety-inducing and hallucinogenic properties of THC. Elderly patients who take too much THC may experience auditory or visual hallucinations, out-of-body sensations, or heightened anxiety.

SUMMARY

Cannabis can relieve symptoms for many conditions. It is important to understand the underlying cause of your condition and to choose the cannabinoid and terpene profile that usually work best for those symptoms. Cannabis can be dosed in a way that the patient does not have to experience any of the mind-altering effects of THC. THC and CBD potentiate each other, and when used together, patients get the very best of both and without being high. The purpose of the endocannabinoid system is to create homeostasis, and when it is not doing the job, our bodies are out of balance and suffer. Cannabis brings relief and healing to many people but not to everyone. Some ailments are not remedied by cannabis. And some patients who experience constant or chronic discomfort may benefit from a little escape from time to time. If you are not bothered by a little psychoactivity and have some quiet time to yourself, then this may be an opportunity to take yourself away from the pain for a few hours—just like a short getaway can be healing and restorative.

Always start with a low dose, and gradually increase it until you experience symptom relief. With cannabis, less is more, so use the least amount necessary. Many patients come back for follow-up still symptomatic. When I ask how much they are taking, more often than not, the answer is “two drops.” Perhaps the fear of taking too much keeps them from increasing, but if two drops is not your dose, then it won’t help. Cannabis, used in low to moderate doses, is healing, not addicting. Use enough but not too much, and allow it to help you to relax, eat, forget, sleep, and—most importantly—feel better!

Chapter 6

Adverse Effects Associated with Cannabis Use for Medical Problems

While not 100 percent risk free, cannabis is amazingly short on side effects. With acute use, most undesirable effects are caused by delta-9 THC, and they are dose related; the higher the amount of THC, the greater the possibility of experiencing an adverse reaction. Some common side effects associated with THC use are dry mouth, dry eyes, reddened eyes, slow pupil response to light, and decreased eye-blink rate. Any adverse effects from too high a dose of THC will resolve once the THC is metabolized and eliminated.[1]

LETHAL DOSE

Although there is an abundance of cannabinoid receptors in the brain, unlike opiates, there is a paucity of receptors in the area of the brain that controls heart rate and respirations.[2] Therefore, none of the direct adverse effects caused by THC are life threatening. It is not possible to consume or inhale enough cannabis to reach the lethal dose—which is approximately 15,000 times higher than the therapeutic dose. According to the Oregon Institute for Cannabis Therapeutics, a nonlethal dose of 92 milligrams per kilogram of THC given intravenously to monkeys is equal to a 154-pound person smoking 3 *pounds* of 1 percent cannabis at one time. This would be more than 1 million times the minimal effective dose and 250,000 times the usual smoked dose. The same person would have to eat 10 pounds of 5 percent hashish at one time to achieve similar nonlethal blood levels.[3] In comparison, doubling an insulin dose or achieving a blood alcohol concentration of 0.4 percent can result in death. The DEA estimates that a person would have to smoke 1,500 pounds of cannabis in 15 minutes to be lethal.[4]

POOR METABOLIZERS

Poor metabolizers are people who are genetically predisposed to clear medications from their system at a slower rate than the average person. Patients who are poor metabolizers of THC or who are on medications that slow down the metabolism of THC are at increased risk of experiencing undesirable effects and at doses that are lower than what would be expected to cause problems.[5] Patients with a history of experiencing many side effects from a variety of medications should consider pharmacogenomics testing. This is usually a saliva test that assesses the activity of enzymes in the liver that are used to metabolize medications. The results of these tests can be helpful in dosing not only cannabis but also other medications that might benefit a patient's condition.

Some medications can interfere with the metabolism of THC by inhibiting the necessary liver enzymes. Taking these medications in close proximity to a cannabis dose may result in higher-than-expected blood levels. While this list is not exhaustive, they include antifungal medications like ketoconazole, fluconazole, and metronidazole; fluoxetine; cimetidine; and erythromycin (see the section "Drug Interactions" later in this chapter).[6]

While cannabidiol (CBD) does not cause intoxicating effects, high doses can cause sedation, diarrhea, and decreased appetite. Medications that can interfere with CBD metabolism include clopidogrel (Plavix), cimetidine, citalopram (Celexa), delavirdine (Rescriptor), efavirenz, felbamate, fluconazole (Diflucan), fluoxetine (Prozac), fluvastatin, fluvoxamine (Luvox), indomethacin (Indocin), isoniazid, ketoconazole, lansoprazole (Prevacid), lovastatin (Mevacor), metronidazole (Flagyl), modafinil (Provigil), paroxetine (Paxil), probenecid, omeprazole (Prilosec), oxcarbazepine (Trileptal), sulfamethoxazole, sertraline (Zoloft), ticlodipine (Ticlid), and topiramate (Topamax).

Using edibles increases the risk of side effects. One of the reasons is that absorption of cannabinoids from the gastrointestinal tract is very unpredictable. A patient might absorb a small portion of a large dose and experience relief and, on another day, take the same dose, absorb a lot more, and feel the undesirable effects of THC. Sometimes the amount of time needed to absorb the medicine is longer than usual, and thinking that they have not taken enough, a patient may take an additional dose, only for everything to kick in hours later. The side effects most often encountered

are anxiety, paranoia, nausea, and sedation, as well as effects on the nervous system that impair memory, balance, reaction time, and dizziness.

INTOXICATION

The intoxicating effect of THC can cause euphoria and enhanced sensory perception—colors may appear to be more vivid, and vision and hearing may sharpen. There may be impaired balance and coordination, and reaction times may be slower. Some varieties of cannabis are energizing and motivating, which can be a benefit, while others may cause sedation.

The intoxicating effect associated with THC can be an adverse effect or a benefit, depending on the condition and goals of the patient. For patients in severe pain, the altered mentation can add to their relief and take their minds off of their discomfort. For others, it can be an annoyance or cause psychic discomfort. Some patients are very sensitive to THC and have described out-of-body experiences.

Many of the side effects associated with cannabis use can be avoided by starting with a very low dose and gradually increasing until the desired response is reached, utilizing a mode of delivery that slows the delivery of THC to the brain, and using plant varieties that have enough CBD to dampen the intoxicating effects of THC.

IMPAIRED DRIVING

Cannabis slows reaction time and impairs short-term memory. With intoxication, fine- and gross-motor coordination are impaired, resulting in clumsiness, and sense of time is altered.[7] All of these things can impair driving. THC concentrations of two to five nanograms per milliliter are associated with substantial driving impairment. Studies show that cannabis users attempt to compensate by driving more slowly and allowing for more distance between them and the preceding vehicle. When paired with alcohol, lane weaving becomes more problematic.[8] Studies have shown that 10 percent of fatal motor vehicle accidents have evidence of cannabis use, and 70 to 90 percent of those also have elevated blood alcohol levels. Combining alcohol with cannabis and driving is dangerous. Cannabis use alone doubles the risk of having an accident. The Insurance Institute for Highway Safety looked at rates of collision claims in Colorado, Oregon, and Washington after recreational cannabis was legalized and reported a 3 percent increase.[9] Another study in the *American Journal of Public Health*

reported no increase in fatalities.[10] Nevertheless, driving is not advised if you are impaired by THC. I advise patients to use a CBD:THC balanced variety of cannabis for daytime use and limit THC-rich strains for evenings when they are in for the night. In legal terms, driving under the influence of cannabis is no different than driving under the influence of alcohol, and if caught, you will be arrested.

PSYCHOSIS

CBD and low doses of THC have antipsychotic effects; however, because of the biphasic effect of cannabis, THC at high doses can cause hallucinations in some patients. This is not a permanent condition, nor should it be construed as the emergence of schizophrenia or a psychotic illness. The symptoms will cease once the THC level is metabolized and eliminated. It was once thought that cannabis could induce psychotic illnesses like schizophrenia, but that has not been proven and is no longer thought to be the case, except in people who are genetically predisposed to develop schizophrenia.[11]

ANXIETY AND PARANOIA

At low doses, THC lowers anxiety; however, at high doses or in patients who are sensitive, THC can precipitate anxiety and paranoia. When highly concentrated waxes, shatters, and vape oils are used, it is very difficult to control the dose, so this type of reaction is likely to occur, especially in cannabis-naïve and elderly patients.

GASTROINTESTINAL EFFECTS

Nausea and vomiting are the more common side effects associated with too much THC. These are typically transient symptoms that resolve once the THC is metabolized and blood levels are lowered. While low to moderate doses of CBD regulate gastrointestinal motility and relieve constipation or diarrhea, excessively high doses of CBD can cause diarrhea. Although CBD lowers gastric acidity and often improves symptoms related to gastroesophageal reflux disorder (GERD), it can also lower gastroesophageal sphincter tone, which may make symptoms worse. In my clinical experience, it is more likely to improve symptoms associated with reflux but is something to consider if GERD symptoms

increase while taking CBD.

SEDATION

This can be a benefit for insomniacs but a negative side effect if daytime alertness is impaired. This can be caused by both THC- and CBD-dominant varieties. Terpenes like myrcene and linalool are relaxing and may contribute to this effect. CBD in low doses can be energizing and may interfere with falling asleep if taken too late in the day. At higher doses, CBD tends to be sedating.[12] There are patients, however, who experience sedation with CBD even at relatively low doses. This typically goes away with continued use. Cannabis that has been sitting around for a while may have higher levels of CBN, a metabolite of THC. CBN is sedating and often found in varieties of cannabis known to help patients fall asleep and stay asleep.

APPETITE

The effect of cannabis on the appetite can be an adverse effect or a benefit, depending on the condition of patient. THC stimulates the appetite; CBD suppresses the appetite.

CARDIOVASCULAR EFFECTS

While cannabis does not have an effect on heart rate and blood pressure in all patients, THC can be associated with an increase in heart rate in patients new to cannabis or who take too high a dose. Blood pressure is typically not affected.

THC can be associated with lowering of heart rate and blood pressure after long-term use. This can potentially cause dizziness or even fainting in patients whose normal systolic pressure is less than 100. Patients on medication for hypertension should monitor their pressure when using cannabis over time. If the pressures decline significantly, an adjustment in the dose of their medication might be warranted. I have seen patients whose blood pressures have normalized with the use of THC over time.

Changes in heart rate could be problematic for patients who have an uncontrolled arrhythmia, when the rate is either too high or too low. Patients with histories of arrhythmias controlled by medication, surgery, or pacemaker appear to tolerate cannabis without incident. I have followed

patients with other cardiac problems, such as congestive heart failure and abnormal ejection fractions, who also do not appear to suffer any ill effects.

The use of cannabis in patients with severe cardiac instability should be avoided or done with great caution. For patients with hypoperfusion issues, which is poor delivery of blood to the heart muscle from severe atherosclerotic disease or decreased cardiac output, lowering blood pressure or heart rate could further decrease the delivery of oxygen to the muscle and cause an ischemic event, or heart attack. While THC might not be the best choice in these patients, studies have shown that patients using CBD benefit from its antioxidant and cardioprotective effects, which have been shown in animal models to minimize the area of ischemic damage to the heart muscle. I encourage patients with heart disease to use high-CBD varieties with very little THC.

RESPIRATORY EFFECTS

Respiratory symptoms can arise, not from the plant itself, but from mechanical irritation to the airways from smoking and vaporizing. Inhaling cannabis can also cause increased mucous production and cough.

In contrast to the smoking of tobacco leaf, it has not been established that smoking cannabis is associated with an increased risk of lung cancer or chronic obstructive pulmonary disease (COPD). It is not known whether the anti-inflammatory, bronchodilation, and antitumor properties play a part. That being said, the products of combustion from burning cannabis are carcinogenic, and the amounts of tar delivered to the lungs is high. I do not typically recommend inhalation as a mode of delivery unless the patient has a condition that demands a rapid onset of action; if that’s the case, I recommend vaporizing instead of smoking. Otherwise, there are other delivery systems—tinctures, lozenges, and transdermal—that are not associated with these side effects. Generally, any symptoms that arise from vaporizing or smoking cannabis resolve once another method of delivery is used.

INFECTION

Cannabis is not an immunosuppressant; therefore, it does not cause patients to be more susceptible to infection. Cannabis *modulates* the autoimmune system by increasing and decreasing various proinflammatory

mediators like tumor necrotic factor (TNF), interferon (INF), and leukokinins (IL), thereby having the ability to mitigate some of the symptoms caused by autoimmune conditions like myasthenia gravis and lupus.

Any cannabis plant, and especially community-acquired cannabis, if contaminated with pathogenic molds and bacteria can cause respiratory infections. This is of special concern for patients with compromised immune systems. Researchers at the University of California, Davis, identified multiple organisms in medical cannabis plants that can cause serious infection in patients with AIDS, leukemia, or lymphoma or those receiving immunosuppressive therapy for other medical conditions (see chapter 4).

FERTILITY

The endocannabinoid system plays a significant role in the reproductive tract, as well. Receptors and endocannabinoids are found throughout the system—from an area of the brain called the hypothalamus that controls the production of sex and reproductive hormones, down to the Leydig and Sertoli cells in the testes and sperm.

It has been well documented that testosterone and the female follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin levels are reduced with heavy THC-rich cannabis use. Low levels of these hormones can negatively affect sperm production and sperm motility.[13] Studies have found downregulation, or decreased synthesis, of anandamide and 2-AG in the sperm of infertile men and, in women with histories of early spontaneous abortions, decreased fatty acid amide hydrolase (FAAH, the enzyme that metabolizes anandamide) activity in maternal lymphocytes.[14]

PREGNANCY

Pregnant women have certainly used cannabis, and there are studies with contradictory conclusions. A 2011–2013 Australian study of 344 Aboriginal women found that those who used cannabis during pregnancy were more likely to have smaller babies and more likely to give birth to babies with low birth weights or babies that were small for gestational age.[15] However, this study was not able to assess doses or control for use of alcohol or other drugs.

In 2016, researchers at the University of Arizona reviewed 24 studies on cannabis use in pregnancy. They concluded that infants of women who used cannabis during pregnancy had an increased incidence of low birth weight and increased risk of being admitted to the neonatal intensive care unit compared to mothers who didn't use cannabis during their pregnancies. Again, most of the studies were not able to exclude concurrent alcohol or tobacco use. The four-year retrospective study of 8,138 women found that 8.4 percent of the subjects used cannabis during pregnancy. The women using cannabis tended to be younger, African American, and with poor prenatal care. They were also more likely to use tobacco, alcohol, and other drugs. When results were adjusted for race, tobacco, alcohol, and other drugs, poor neonatal outcome was not significantly higher among those who used cannabis during pregnancy.[16] In yet another study of 106 women who used cannabis during pregnancy, once controlled for use of other substances, researchers were unable to identify adverse neonatal outcomes.[17]

Neonatal outcome does not always predict long-term consequences of behavior and exposures during pregnancy. Until future studies are able to show that cannabis has no effect on birth weight, perinatal health, fetal neurodevelopment, childhood developmental milestones, and other sequelae, I will not make cannabis recommendations for pregnant or nursing women. Until we know that there are no risks associated with perinatal exposure to THC, or even CBD, I prefer to err on the side of caution.

TESTICULAR CANCER

In earlier studies, there appeared to be an association with increased risk of testicular cancer and heavy cannabis use in younger men.[18] However, a 2015 systematic review of the literature did not conclude that there was a strong association with cannabis smoking and testicular cancer.[19] The association between heavy cannabis use and testicular cancer remains inconclusive.

TOLERANCE

Tolerance occurs when cannabis is used over an extended period of time, especially at high doses. When the endocannabinoid system sees a lot of cannabinoids, it interprets the high levels as an indication to downregulate,

or shut down, cannabinoid receptors. When the system is downregulated, it takes higher doses to achieve similar effects. This occurs in different areas of the brain at different rates. For example, the effect of THC on memory loss in chronic cannabis users tends to improve with time, but the experience of the euphoric high continues. If the tolerance were the same throughout the brain, then memory would no longer be affected and the euphoric response would go away, but that does not happen.[20] When health-care providers treat pain with NSAIDs, opiates, and other types of medication, the doses are gradually increased if previous doses no longer are effective. With cannabis, the approach to tolerance is just the opposite. If patients discontinue using cannabis for a short period of time, a mere three or four days, then the system will increase the number of receptors to make up for the lower levels of cannabinoids.

I suggest to my patients that they not medicate every day if they have an alternative medication to use on off days. I also recommend that they use the lowest dose necessary to alleviate their symptoms. Just doing these two things often prevents tolerance from developing. If after time they feel that the dose they have been using is no longer effective, then it may be time to stop cannabis use for three or four days and then start back at a dose that is about a third of the previous dose. Starting there, I have them again titrate their doses, increasing gradually by one drop or one puff at a time until they experience maximum relief. More times than not, that new dose is actually lower, not higher, than the dose that was no longer effective (see textbox 6.1).

Textbox 6.1 Case Study

Early in my career in medical cannabis, I evaluated a retired gentleman with chronic low-back pain who was smoking almost every bit of the maximum four-ounce allotment of cannabis per month. Despite this heavy use, his back pain was no longer responding. Having to dose every two to three hours was time consuming and very expensive, and he was not feeling better. I convinced him to stop using cannabis for just three days and advised him to treat his symptoms with Naprosyn and cyclobenzaprine for those three days and a topical cannabis salve that could be applied in thin layers as often as needed instead. He was advised to resume his cannabis use at one-third the dose he was using before. He was also advised to take one to two puffs and to wait 10 to 15 minutes before taking another puff. A few weeks later, I followed up with him, and he was

feeling much better; his back pain was markedly improved and with a much smaller amount of cannabis.

NERVOUS SYSTEM

Lethargy; slowed reaction time; dysphoria; dizziness; altered sense of time; and impaired balance, coordination, short-term and episodic memory, problem-solving skills, and focus can occur with higher doses of THC. It is important for patients to note that they are not experiencing any of these effects before deciding to drive, operate any type of machinery, or make legal decisions. These side effects will also increase the risk of a patient falling and must be taken into consideration when recommending cannabis to elderly patients or patients with impaired balance.

There is data to suggest that excessive use of high doses of delta-9 THC over prolonged periods affects episodic memory and has a negative impact on a person's ability to take on new information (e.g., the loss of IQ points); there are also studies that refute this.[21] Again, these adverse effects have not been identified in those who use cannabis in low to moderate doses for medical reasons and is more commonly ascribed to long-term, heavy recreational use. When these adverse cognitive effects do occur, studies indicate that they resolve with subsequent abstinence.[22]

CBD does not cause these effects, and patients using CBD-dominant varieties of cannabis, even with moderate amounts of THC, do not typically experience mental impairment. CBD's neuroprotective properties may protect against the neurotoxicity of THC. Every person is different, however, and some patients experience mental impairment, even when CBD is present. You also have to keep in mind that mistakes happen. You may have a product that has more THC in it than is recorded on the label. Always try a new product, even if it has the same name or cannabinoid profile, at a time when you will not need to drive, operate heavy or dangerous equipment, or make legal decisions.

Less common but possible side effects from THC include changes in blood pressure or heart rate and hallucinations.

NEURODEVELOPMENTAL

Cannabis has an exceedingly high safety profile. There are very few documented side effects associated with cannabis use; those pertain to a

dose response to delta-9 THC, and they have been discussed in this chapter.

One large concern expressed in anticannabis legislation and by the American Academy of Pediatrics has been that legalization would increase access and use for adolescents, whose brains are still developing and are at increased risk of neurodevelopmental changes—impaired short-term memory and decreased concentration, attention span, and problem-solving skills, all of which interfere with learning.[23] Another concern is alterations in motor control, coordination, judgment, reaction time, and tracking ability, which have the potential to increase the incidence of motor vehicle and other types of accidents.[24]

Interestingly, since the legalization of medical cannabis at state levels, adolescent cannabis use and prevalence of cannabis use disorder in adolescents has gone down. According to the Substance Abuse and Mental Health Services Administration's December 2015 report, teen use of cannabis in all 50 states did not change except in three states—Ohio, Hawaii, and Rhode Island—where teen use decreased.[25] According to the Colorado Department of Health 2015 Healthy Kids Colorado survey, 21.2 percent of adolescents used marijuana in 2015, two full years after cannabis became legal for medical use, down from 25 percent in 2009, before medical use was legalized. It is also noteworthy that cannabis use among adolescents in Colorado is just below the national average of 21.7 percent.[26]

In 2013, the National Institute on Drug Abuse published a statement on adolescent cannabis use: "Regular marijuana use in adolescence is part of a cluster of behaviors that can produce enduring detrimental effects and alter the trajectory of a young person's life—thwarting his or her potential. Beyond potentially lowering IQ, teen marijuana use is linked to school dropout, other drug use, mental health problems, etc."[27]

Synaptic remodeling and pruning continues in humans until about age 25. The brain is laying down needed pathways and clearing away those that are not necessary.[28] There is equivocal evidence that delta-9 THC has a negative effect on this process.[29] Magnetic resonance imaging studies have shown reductions in the volumes of the hippocampus, amygdala, and cerebellum in long-term, heavy, recreational users of THC when compared to nonusers.[30] And it has also been shown that users who started before the age of 17 have a smaller ratio of cortical gray to white matter in the brain. This phenomenon has not been described in patients whose doses are

typical for medical use. While these studies implicate the chronic use of cannabis in deleterious effects on the morphology of brain structures that control emotion, memory, learning, and executive function, there is contradictory evidence that it does not.[31]

Over the last few years, I have evaluated thousands of adults seeking recommendations for the use of medical cannabis. I have seen many young men who are highly functioning adults in their 30s and 40s who admit to using cannabis as early as 16 and 17 years old. Some used it to treat painful sports injuries, others for severe anxiety, and others for stress reduction and relaxation. Perhaps their use was symptom-directed, which meant that the doses they used were low to moderate. They appear to be fully functioning, successful individuals. While formal neuroeducational testing has not been done, these patients have earned advanced degrees and have continued to function in demanding professions, including restaurant owners and executive chefs, attorneys, computer programmers, software developers, college professors, medical specialists, and accountants, to name a few.

On the other hand, there are patients, both male and female, who have an affect, or look, that I have noticed in daily cannabis users, in which speech is slower and reaction time to questions appears to be decreased. It is difficult to tell if they are acutely intoxicated by cannabis or if this is the effect of long-term cannabis use. I suspect that it is a combination of both.

I believe that there can be long-term neurological consequences associated with chronic cannabis use, but from my clinical experience, it appears to be most pronounced in patients who are using cannabis as an intoxicant and at higher and more frequent doses. In some patients, it has affected their lives negatively with regard to legal problems or job loss because they tested positive for drugs. There are many patients, however, working in areas where drug testing is not a factor, and they do not have any apparent issues.

Three psychiatric disorders commonly seen in pediatrics—obsessive-compulsive disorder, attention deficit disorder, and Tourette syndrome—are characterized by abnormal functioning of the neural pathways that connect the frontal lobe with the basal ganglia, resulting in impaired self-regulation. These happen to be three conditions that have been reported, anecdotally, to respond to cannabis therapy. We must consider that abnormalities in this area of the brain may influence why some adolescents choose to use cannabis at an early age.

We are still faced with what comes first: the proverbial chicken or egg? Does early use of cannabis cause abnormalities in the developing brain, or do abnormalities in the developing brain lead to early cannabis self-medication? I don't think these questions have been adequately addressed. They will be difficult to answer as long as cannabis's Schedule I status impedes research focused on benefits. As it stands, the only research on cannabis that can be conducted by the National Institute on Drug Abuse has to be focused on demonstrating that its use is detrimental. Until these questions are answered, I think we have to rethink our approach to young people who experiment with cannabis and consider that perhaps there is an underlying issue that leads them to seek relief from an illegal substance. Such adolescents should be evaluated, diagnosed, and treated, not punished. We also have to continue to consider that there may be detrimental effects on neurodevelopment and carefully weigh the risks and benefits when making recommendations for adolescents and young adults.[32] The current evidence suggests that neurodevelopmental impairment from cannabis is related to chronic and heavy use of THC.

It stands to reason that some behavior issues may lead to experimentation with drugs and that cannabis, being readily available, as are alcohol and tobacco, is easily acquired by this population. Prior assertions that cannabis use in and of itself leads to the use of more dangerous drugs have certainly been dispelled. There has been no establishment of cause and effect. The 2013 statement issued by the director of the National Institute on Drug Abuse would lead one to believe that cannabis causes the behavior, but it is well known that people who abuse drugs start with substances that are readily available. Those substances are usually cigarettes, alcohol, and marijuana. Given that, one could say that tobacco use in adolescence leads to drug abuse later in life. One also has to consider that people who may be more impulsive or more willing to take such risks as using illegal substances could possibly be doing so because of structural or neurochemical differences in the brain. While the jury is still out on the long-term effects of chronic exposure to cannabis, there is not much doubt that THC has an effect on short-term and episodic memory, time perception, sensory perception, and coordination and that the risks of these side effects must be outweighed by the benefits of its use.

DRUG INTERACTIONS

Just like any other medication, it is important to know which medications

might affect cannabis metabolism and which medications might be affected by the use of cannabis. When medications are absorbed from the gastrointestinal tract, they are metabolized in the liver by an enzyme system known as cytochrome P450. When a medication is metabolized at a slower-than-expected rate, the normal doses that are usually well tolerated can cause higher-than-expected blood levels and can lead to undesirable side effects. Another consideration is that, with some medications, it is the metabolite, not the drug itself, that is the active agent. In those cases, if cannabis interferes with the metabolism, there will be lower-than-expected levels of the active agent. This may result in subtherapeutic levels, decreased efficacy, or exacerbation of symptoms.

When cannabis is swallowed, eaten, or given via an indwelling catheter in the stomach or feeding tube, it is absorbed from the intestines and goes to the liver, where the enzymes metabolize the drug. This is referred to as the hepatic first pass. Different components of cannabis are metabolized by different enzymes. CBD is metabolized by CYP3A4 and CYP2C19; THC is metabolized by CYP3A4 and CYP2C9.[33] When CBD is metabolized, a lot of CYP3A4 is used up—leaving little to metabolize other medications.[34] When patients take other medications that need CYP3A4 too closely to CBD, there may not be enough enzyme left to adequately metabolize other drugs. The enzyme 3A4 is used to metabolize approximately 65 percent of the medications for which health-care providers write prescriptions, as well as many over-the-counter medications. Because CBD, in particular, uses up a lot of that enzyme, if it is taken in close proximity to medications that need that enzyme, it can cause higher plasma levels than expected. This is especially important when patients are taking medications like antidepressants, blood thinners, and cholesterol-lowering medications like statins. CBD can increase the sedative effect and mental confusion of benzodiazepines and can be a problem for elderly patients and those who have an increased risk of falling due to physical or mental limitations. However, taking cannabis in close proximity to benzodiazepines does not increase the risk of respiratory depression as is the case when opiates are taken with such benzodiazepines as alprazolam and diazepam.

THC uses CYP3A4 and CYP2C9 but not to the extent that CBD uses CYP3A4. THC also induces or activates the CYP1A2 enzyme. When this enzyme is activated, serum levels of the medications metabolized by that enzyme may be lower than expected. Some of the medications

metabolized by this enzyme are chlorpromazine, clozapine, cyclobenzaprine, olanzapine, duloxetine, haloperidol, and naproxen.[35] Delta-9 THC also has a significant additive effect when combined with alcohol and barbiturates.

While cannabis may not affect all of the medications in these classes, when in doubt, I advise spacing cannabis one and a half to two hours from the tricyclic antidepressants, MAO inhibitors, antiepilepsy drugs, benzodiazepines, statins, proton pump inhibitors, beta blockers, and anticoagulants. This is especially important when taking medications that use more than one of these enzymes for metabolic clearance.

It has been documented that valproic acid (Depakote) and clobazam (Onfi) levels can be affected by CBD. Levels of any antiepilepsy drugs should be monitored, and especially when taking clobazam.

While taking these medications is not a contraindication to using cannabis products, and many people who use cannabis do not experience adverse effects from medications, it is best to err on the side of caution and space your medication when possible. The appendix at the end of this book lists some known medication interactions but should not be considered complete. There may be other medications that are metabolized by these enzymes that are not listed. Your recommending physician or provider should review your medication list and make note of any that should be taken two hours from your cannabis dose.

There are also medications that can interfere with the metabolism of THC and CBD (see appendix). These medications can increase the plasma levels of cannabis. Medications that inhibit 3A4 may increase levels of both CBD and delta-9 THC. Inhibitors of 2C9 may increase levels of CBD, and inhibitors of 2C19 may interfere with the metabolism of delta-9 THC and increase its plasma levels, which will increase the risk of adverse effects.[36]

Particular care must be taken when giving CBD to seizure patients. Having followed many patients who are taking multiple medications, I have not seen many problems with drug interactions, but fluctuations in plasma levels do occur in either direction. Watch for increases with Depakote, Onfi, Keppra, felbamate, topiramate, and phenobarbital levels and decreases with lamotrigine, clonazepam, lacosamide, and rufinamide levels. But remember, levels can fluctuate in either direction.[37]

POSSIBLE CONSEQUENCES OF OVERUSE

Substance Use Disorder

Substance use disorder is far more prevalent than cannabis addiction and can affect as many as 30 percent of people who use cannabis. Cannabis use disorder and addiction are most common in young males between the ages of 18 and 30, and given the widespread availability of cannabis with high concentrations of THC, I suspect it is underreported. People who use cannabis at these high concentrations may be seeking the euphoric effect of the plant and may not be using cannabis for medical conditions. Patients suffering from bipolar affective disorder are at increased risk of developing a substance use disorder, so care should be taken to use low-THC varieties along with careful monitoring by the patient's mental-health provider.

Symptoms of substance use disorder include:

- taking larger amounts of a substance or for longer than intended;
- repeatedly failing to use less or quit;
- dedicating a lot of time to acquiring or using;
- having cravings or urges;
- giving up activities in order to use the substance;
- continuing to use the substance even when it is causing problems with work, school, or home life;
- using the substance even if it puts you in dangerous situations;
- having physical or psychological problems caused or made worse by the substance;
- needing more of the substance to get the effect you want; and
- having withdrawal symptoms that are relieved by using the substance.

Substance use disorder is rated mild if the patient has two to three symptoms, moderate with four to five symptoms, and severe with six or more symptoms.[38]

The amount and frequency of THC use is directly proportionate to the likelihood of cannabis use becoming a problem; frequently using high doses increases your risk.[39] Medical cannabis dispensaries commonly sell highly concentrated waxes, shatters, budders, and other products that can have THC concentrations as high as 96 percent. Cannabis flower concentrations are also high, at 10 to 26 percent; in contrast, the average THC content in confiscated cannabis in the 1990s was about 3.7 percent.[40]

Cannabis, especially THC, works better for most ailments at low to moderate doses, so there is no reason to use high-THC-concentration products. Using small doses of a tincture two to four times a day or vaporizing less than an ounce of flower per month with breaks here and there is not likely to cause tolerance, dependence, or addiction. This is not to say that some patients require higher doses to alleviate their symptoms, but it's important to use the least amount necessary.

Cannabis addiction rates are at about 9 to 10 percent and are considered relatively low when compared to other substances that commonly cause addiction, like caffeine, tobacco, and alcohol. For chronic pain patients, THC is relatively ineffective at high doses, and the patients who need high doses probably have either developed tolerance or may be rapid metabolizers, meaning that they metabolize cannabis at such a rapid rate that it takes higher-than-usual doses to obtain a therapeutic blood level.

In 1994, Jack Henningfield of the National Institute on Drug Abuse and Neal L. Benowitz at the University of California, San Francisco, conducted a study on nicotine addiction. They ranked six commonly abused drugs in order of severity according to five criteria: dependence, withdrawal, reinforcement, tolerance, and intoxication (see tables 6.1 and 6.2). Cannabis ranked sixth, or the least likely to cause either serious withdrawal symptoms or dependence, when compared to alcohol, nicotine, heroin, cocaine, and caffeine. Cannabis users who are males between the ages of 18 and 24 have the greatest risk of becoming addicted, and that rate has remained at about 9 percent.[41]

Table 6.1 Rating Scales of Six Commonly Abused Drugs (Henningfield)*

Substance	*Dependence*	*Withdrawal*	*Reinforcement*	*Tolerance*	*Intoxication*
Nicotine	1	1	4	2	5
Heroin	2	2	2	1	2
Cocaine	3	3	1	4	3
Alcohol	4	4	3	3	1
Caffeine	5	5	6	5	6
Cannabis	6	6	5	6	4

Source: N. L. Benowitz and J. E. Henningfield, "Establishing a Nicotine Threshold for Addiction," *New England Journal of Medicine* 331, no. 2 (1994): 123–25.
*1 = most serious, 6 = least serious.

Table 6.2 Rating Scales of Six Commonly Abused Drugs (Benowitz)*

Substance	*Dependence*	*Withdrawal*	*Reinforcement*	*Tolerance*	*Intoxication*
Nicotine	1	3**	4	4**	6
Heroin	2	2	2	2	2
Cocaine	3	3**	1	1	3
Alcohol	4	1	3	4**	1
Caffeine	5	4	5	3	5
Cannabis	6	5	6	5	4

Source: N. L. Benowitz and J. E. Henningfield, "Establishing a Nicotine Threshold for Addiction," *New England Journal of Medicine* 331, no. 2 (1994): 123–25.
*1 = most serious, 6 = least serious.
**equal ratings.

Amotivational Syndrome

This syndrome is just what it says: Patients are complacent and unmotivated. While this is seen clinically in some heavy cannabis users, causality has not been established, meaning it has not been determined if patients with this condition turn to cannabis or if cannabis causes the problem. It has been described in patients with cannabis use disorder and depression and as a side effect of serotonin reuptake inhibitors. This is another possible effect of overuse and has not been described as an adverse consequence of medicinal use.

Cannabinoid Hyperemesis Syndrome

Chronic nausea and vomiting can be a symptom of cannabinoid hyperemesis syndrome. This syndrome is typically seen in young men who are recreational users or are self-medicating and is a consequence of using large amounts of cannabis over an extended period of time. This is not considered an adverse effect of medical use but a symptom of cannabis use disorder. Patients with this condition typically find relief from the nausea by taking frequent hot showers. It is thought that activation of the heat receptors (TRPV1) in the skin play a role in alleviating the symptoms. Capsaicin cream, which also activates those heat receptors, has also been found to be effective in alleviating these symptoms.[42] Patients with this condition will improve if they abstain from using cannabis.

SUMMARY

When cannabis varieties that contain both CBD and THC are started at low doses and gradually increased until symptoms are alleviated, it is usually very well tolerated and with minimal or no adverse effects. Adverse effects are typically associated with high-THC doses, which will resolve once the THC is metabolized and eliminated. With the possible exception of excessive use, particularly in young, heavy cannabis users, the adverse effects associated with THC are not permanent. CBD and THC synergize each other’s beneficial effects, and CBD mitigates the intoxicating effect of THC while also preventing THC’s effect on memory, balance, reaction time, and coordination.

Chapter 7

First Doctor's Visit

Start with Your Provider

If you are interested in trying medical cannabis but don't know where to start, I encourage you to discuss it first with your primary- or specialty-care provider. Some doctors support cannabis therapy and are able to write the recommendation for their established patients. Others support the idea but are unable to write the recommendation themselves because of where they work. Typically, the large medical businesses, HMOs, and university health systems have made a business decision not to allow their doctors and providers to write recommendations, so it may not be an option for them, even if they think it's a good idea. These providers may have a colleague or know of a doctor that other patients have seen and may be happy to give you a name or even a formal referral.

There are other providers who don't know much about the plant and how it could help your condition, or they have an unfounded fear that they could lose their medical or DEA license if they recommend cannabis. They may not want to discuss it at all. If that's the case, don't be discouraged. Your doctor is not likely to fire you from their practice. If you are comfortable, just inform them that you are using medical cannabis to help alleviate your symptoms and that you are being followed by a doctor who specializes in cannabis medicine. With that knowledge, as they see you improve, they may be more open to discussing it with subsequent patients.

Cannabis is no different than any other drug, vitamin, or herbal supplement; drug interactions can occur, and I like my patients to inform their other providers that they are using cannabis for that reason. I also like other doctors to see how cannabis is helping their patients improve. Seeing improvement may affect how they look at cannabis, and they may be more open to supporting other patients who wish to try it. Some pain management centers will not continue opiate therapy if their patients test positive for THC. There are, however, some pain management doctors who realize that cannabis can help their patient's symptoms as well as alleviate some withdrawal symptoms, so they support their patient's use of

cannabis while in the process of weaning off opiates.

If your doctor is unable to write a recommendation for you, then he or she may be able to refer you to a colleague who is knowledgeable and reputable to assist with your recommendation and management. There are several websites that publish the names of physicians who specialize in cannabis medicine, including the Society of Cannabis Clinicians and the United Patients Group. If there is no doctor available in your area, then try an online search.

HOW TO DECIDE ON A CANNABIS DOCTOR

When deciding on a medical cannabis provider, consider whether this is a doctor who specializes in cannabis or if it is a business with multiple locations that just provides recommendations. The latter tend to be cheaper, quick, in-and-out visits without much review of your medical problems, prior treatments, lifestyle, nutritional status, or other aspects that may be affecting your medical condition. If you are cannabis savvy and have a relatively uncomplicated medical history, then these may be the best places to be seen. There is generally little offered in terms of medication guidance, dosing support, or follow-up. This may be all that is needed for patients who have had experience with cannabis in the past and have knowledge of what types of cannabis are best for treating their symptoms and how to avoid adverse effects from cannabis. For pediatric, geriatric, and adult patients with complicated medical histories or who have no experience with cannabis, a cannabis specialist may be a more appropriate choice. The consultations are typically a little more expensive, but you have a lot more time with the doctor, who will review your medications, cardiovascular status, and any mental-health issues that may affect how you respond to cannabis. Those appointments are usually longer—typically 60 to 90 minutes—and patients receive much more individualized information.

When you call for your appointment, find out how much time you should allot for the visit. This will give you some idea as to whether this provider will be a good fit. Again, short visits are not inappropriate for otherwise healthy adults with arthritic pain or insomnia who are not taking other medications, but they are not recommended for children, elderly patients, patients with multiple medical problems, or those who have never used cannabis in the past. In my practice and in practices similar to mine, it is unusual for a new patient to be in and out in less than an hour. I have seen

many patients who make appointments to see me *after* receiving their recommendations from another provider because they leave uninformed or confused.

For pediatric, geriatric, cannabis-naïve, and adult patients with complicated medical problems who are in need of more education, explanation, guidance, and follow-up, look for providers who have their own practices and specialize in cannabinoid medicine. These doctors are also often knowledgeable in alternative and complimentary medicine and therapeutics and can help you beyond a mere cannabis recommendation and "see you next year."

PREPARING FOR YOUR VISIT

Ask if there is any type of registration with the state or county that needs to be done prior to your visit. Regulations vary from state to state. In Maryland, patients register with the Maryland Medical Cannabis Commission and are issued a number that the provider needs in order to complete the patient's certification. In DC, the patient has to see the provider, who inputs the patient's information, which generates a number that is needed in order for the patient to apply for a card from the health department. In California, the doctor sees the patient and issues the certification without the patient having to register with a government agency.

Ask if medical records are necessary and if they need to be faxed prior to your appointment or just brought to the appointment. Ask if the provider will be able to recommend the type of cannabis to use, how to dose, and the best mode of delivery for your condition and be available to answer questions or make dosing adjustments after the visit. If the answer to any of those questions is no, then this is not the place for an inexperienced or complicated patient but may be adequate for patients who don't require much support. Ask if the office accepts other forms of payment besides cash. Can the doctor or practitioner take care of any letters that might be needed for school or work to explain your need for medical cannabis? These are questions that can be answered before scheduling an appointment.

WHEN YOU ARRIVE

When you arrive at the doctor's office, is it clean and professional, or does

it look like it is a rented room for the day? Is the staff courteous? Does anyone on the staff appear to be impaired (stoned)? You will have to determine whether this practice is a good fit for you.

You should expect to complete a medical history form and sign HIPAA papers. You may also be asked to read and sign a list of disclosures regarding the use of cannabis as a medicine and its legal status, risks, and possible adverse reactions. Once you are registered with the practice, vital signs are taken, and weight, height, blood pressure, and pulse should be recorded.

YOUR VISIT WITH THE DOCTOR

If you bring records documenting your condition, then the provider does not have to rely on their own expertise in making the diagnosis and may not feel compelled to examine you for that particular ailment. The provider is then relying on the expertise of the diagnosing practitioner and is determining whether your condition would be reasonably expected to improve with the use of cannabis. The doctor should also review all of your current medications and prior treatments.

The Good-Faith Physical Exam

Providers are required to perform a good-faith physical exam. This does not mean that the provider has to perform a complete physical. The exam may be the doctor's observation of you and, more importantly, an assessment of your mental status. The provider should be able to determine whether you are at increased risk for a cannabis use disorder or cardiovascular instability because these are the areas that would be most adversely affected by using cannabis.

Some providers will just talk to you. Others will examine your heart and lungs; others may do a more complete physical. How much of a hands-on exam is needed is determined by the doctor. If you are seeing a doctor who specializes in your condition, then you should expect a more focused exam. If your condition is outside the scope of that doctor's expertise, then it may be more of a visual assessment.

Regardless of the extent of the exam, in most states, the provider should be physically present, except for special circumstances where patients are not physically able to come to the office (hospice or ventilator dependence, for example). In some states, like California, Nevada, and New York, telemedicine visits are permitted.

Benefits versus Risks

When I meet with a patient for the first time, I try to get a clear idea of the patient's or family's goals and expectations and determine whether cannabis is a reasonable tool to add to their health-care toolbox. I then talk about the endocannabinoid system and how it regulates systems in the body. Your provider should be able to tell you whether it is a reasonable expectation that cannabis might help and what possible adverse events or drug interactions might occur—a risk-versus-benefit analysis (see chapter 6 for more on risks).

Guidance

If the provider is knowledgeable in the types of products that are available in your area, then they should be able to suggest what things might be more beneficial and what types of products should be avoided. The very young and very old should be discouraged from using high concentrations of THC, while patients who are rapid metabolizers of THC may require higher-than-usual doses. Not all doctors have this knowledge or are comfortable making dosing recommendations. If this is information you would like to receive from a provider and not from a potentially medically untrained person at the dispensary, then it's important to ask about this at the time you schedule your appointment.

Once your provider has made an assessment and determined that you might indeed benefit from cannabis therapy, they will complete whatever paperwork is required by your state or county so that you will have access to dispensary medicine.

Return Visits and Follow-Up Care

The frequency and intervals of follow-up care depend on the age and condition of the patient and are at the discretion of the provider. I like to have sicker, more complicated, and younger patients return in six to eight weeks, although there may be some who should follow up in as little as three weeks. Other patients are asked to return in three to four months, and some seasoned patients who are stable and doing well are seen annually or semiannually.

Your provider may be able to offer telemedicine follow-up visits as a convenience if you have many medical appointments or have difficulty ambulating. I find that telemedicine visits are less disruptive for families

with severely autistic children, where any change in routine can be distressing to the patient.

Whether in office or via telemedicine, the provider should follow how you are responding or not responding and assess for possible adverse reactions. They should also be available to answer any questions or concerns about dosing that may occur between visits.

Chapter 8

Ways to Medicate

Traditionally, we think of smoking as the way to get marijuana into our system. For recreational use, especially when not legal on the state level, smoking was the easiest method; it is part of the ritual of packing a bowl or rolling a joint and sharing it with friends. Advances in the medical use of cannabis have brought changes in how the drug can be administered. Vaporization heats cannabis to a specific temperature, called boiling points, causing the cannabinoids and terpenes to evaporate into a vapor that can be inhaled. This eliminates the toxic by-products of traditional inhalation while delivering targeted results with a more rapid onset. Capsules are filled with a specified dosage and taken orally. Cannabis can also be consumed as an "infused edible." This method is the "pot brownie" method; the prescribed dosage is added to candy, cookies, or even drinks to achieve a longer-lasting effect.

Your first trip to a dispensary, where cannabis is sold, will likely be confusing. Like anything else, it's all about educating yourself. Let's start with the taxonomy. *Cannabis* is the name of the genus. It is a member of the Cannabaceae family and a cousin of hops. It is generally divided into the drug-type and the fibrous-type, which includes hemp and has very low amounts of THC. At the dispensary, you will learn about cannabis varieties, or strains, with creative names like OG Kush, Blue Dream, and White Widow.

When I started interviewing medical cannabis patients a few years ago, I would ask my patients about the types of cannabis they were using. The first thing they would say is "I use indicas at night and sativas during the day," or "I stay away from sativas because they make me anxious," or "I don't like indicas because . . ." If I pushed further, they would make references to plants called MediHaze, ACDC, Green Crack, Cannatonic, Sour Diesel, Girl Scout Cookie, Granddaddy Purple, Purple Erkle, and some that modesty prevents me from mentioning in mixed company! Even

as I became more familiar with some of the different varieties and their effects on most patients, it was several months more before I even considered mentioning some of the names because, quite frankly, they just didn't sound very professional. I thought to myself, "Why do they have to have such crazy names?" The first time I suggested Granddaddy Purple to a patient, I think I laughed out loud. I continued to skirt the issue for a while longer until I could actually say the name with a straight face. I started by only mentioning the names with more cannabis-savvy patients. For my more mature first-timers, I would preface my suggestions with, "I know the name sounds a little silly, but . . ."

Many people emphasize whether a plant is a sativa, hybrid, or indica. The generalized effect of these plants has changed over the years. One hundred years ago, indicas were known to be energizing and sativas sedating. That changed because of so much crossbreeding in the 1980s and 1990s, and those generalizations flip-flopped such that sativas have become more energizing and indicas have a more sedating effect. Well, now with even more crossbreeding, there's not much you can hang your hat on about the effects of a plant based solely on its classification. Generally speaking, those effects are somewhat characteristic, but the only thing you can be sure of is that the sativa was a tall, skinny plant with narrow leaves, and the indica is a short, bushy plant with wide leaves.[1]

Some of the more colorful names are now going by the wayside. The Cookie Drizzle seed planted in Colorado will probably be different from the plant that sprouts from the same seed in Oregon. How much UV light the plant receives, the temperature, the ambient humidity, soil nutrients, what's in the water, the time of day it is harvested, and so many other factors influence what cannabinoids and terpenes are produced. Even relying on the cannabinoid profile can be somewhat deceiving because there is more to how a plant will affect a person than just how much CBD or THC is in it. The terpenes and flavonoids also influence the effects, and there may even be other substances that we are not yet aware of. While the name may give some hint to the genetics of the plant, it will not always predict its effects.

Generally speaking, varieties that have *Purple* in the name tend to be relaxing pain relievers and promote sleep, but that is not *always* the case. Names with citrus fruits like "Lemon Drizzle" and "Orange Crush" may have high levels of the terpene limonene, are usually uplifting, and help relieve depression as well as pain. Pain-relieving effects are especially

likely when limonene is in combination with beta-caryophyllene.

It is best to ask the person helping you at the dispensary what they know about a particular strain. They cannot depend on what they have read on websites that rate this variety in another part of the country. There are plenty of cannabis users in any given locale who are trying these different plants and writing reviews. Usually the budtenders (the dispensary personnel who wait on patients) have some knowledge as to the effect it has on most people. If you research a plant variety online, then it is imperative that you input your location, or you may be reading about a Canna-tsu in California that could be quite different from the Canna-tsu grown in Maine.

We are starting to see more and more that processors (the people who make the oils, tinctures, and edibles) are labeling their products with terms that convey the overall effect of that particular plant. That makes it much easier for the recommending provider, dispensary personnel, and patient to choose a medicine that is most likely to address a particular symptom. With this type of labeling, you will not know the name of the plant or plants used to make the product, but you will have an idea about its overall effect.

KEEPING TRACK OF WHAT YOU USE AND HOW YOU RESPOND

Even with some knowledge of how most other people respond is no guarantee that you will experience the same effect. Everyone is unique and responds differently, so I encourage my patients to try different varieties to see what works best. It’s important to keep a record of what is being used, what is in it, how much is needed to alleviate symptoms, and what the effects are.

Many patients who are new to cannabis are unsure of where to start. Their first dispensary experience may be overwhelming for them, especially with all the different strains and products offered at the counter. On top of feeling confused, they may be anxious or nervous about starting their treatment; the stigma of marijuana is still common today, especially among older generations. New patients often have no idea what to expect. The key to overcoming this is to be in control of your treatment. Hopefully your doctor will have had a discussion about what type of cannabis might be best for your condition. When you visit the dispensary, share that

information with the budtender, or patient care specialist, as some prefer to be called. In some markets, you may actually have the opportunity to speak with a health-care professional, like a pharmacist or nurse, but for the most part, budtenders are not medically trained and have varying levels of knowledge of the available cannabis products.

Patients should keep a log of the types of cannabis they try and record their experiences so they can learn (and remember) what works for them and what doesn't. Whenever a new patient comes into my office, I refer them to a free tool, Releaf App, that was developed for this exact purpose.[2] This app allows patients to log their sessions with cannabis in real time and record key details, including dosing, ingestion method, side effects, feelings, notes, and changes in symptom levels. The data from these sessions is compiled into reports that can be shared with your doctor to assess treatment progress. These reports also help patients make better decisions about their cannabis purchases and future treatment sessions. For example, a patient could find that a particular strain successfully treated their depression but also made them feel active and energized. Knowing this will help the patient make good choices about what to use during the day versus before bedtime.

Recording the cannabinoid and terpene profiles makes it easier to choose similar strains, in case the dispensary is sold out of that variety in the future or if a grower may have discarded a harvest because of mold or some other problem. When you find something that really works, go back as soon as you can and stock up. Flower will not keep as long; if present, the THC will convert to CBN, making the plant more sedating. Tinctures have a longer shelf life. If kept in a dark, cool place, tinctures can last for several months. If you need to store it for longer, keep it in the refrigerator.

DECIDING ON YOUR DELIVERY SYSTEM

Most people are familiar with cannabis being smoked in a joint, pipe, or bong or being eaten in a brownie; however, there are several other ways to use cannabis, and patients sometimes experience better results with one particular method or by combining methods.

Delivery systems are broadly categorized as inhalation, edible, oral, sublingual, topical, and rectal/vaginal. It is not uncommon for patients to use more than one method to achieve maximum results. It's important to try a variety of methods to find one that works best for you, especially if you are not experiencing complete relief from your symptoms.

When it comes to dosing, there are no clinical studies, so there are no therapeutic ranges. While most patients respond to THC doses in the 2.5- to 15-milligram range and CBD in the 10- to 40-milligram range, each person responds to cannabis differently, and many patients need far lower or much higher doses. It's always best to start with a very small dose and increase it gradually until you experience the maximum effect. The maximum effect is not always going to mean that you are symptom free. It may mean that your pain level is reduced or your seizures or migraines are less frequent. It is up to you to gradually increase your dose until you experience the most relief. So how do you know what the maximum relief is?

THE BIPHASIC EFFECT

Cannabis has what is known as a biphasic effect, which means that a medicine alleviates symptoms at lower doses but can cause symptoms to worsen if too much is taken. In other words, as you get into higher doses, the effectiveness may decrease or actually make symptoms worse. As you increase your dose, your symptoms might decrease but only to a point some refer to as the sweet spot. If you continue to increase your dose, then you may find that your pain increases or your seizures become more frequent (see textbox 8.1). With each type of cannabis medicine, it is important to wait the appropriate amount of time to see how effective that dose is at alleviating your symptoms; for example, 20 minutes for sublingual (under the tongue) delivery, 10 minutes for inhalation, and 5 minutes for topicals.

Textbox 8.1 Joan

Joan has chronic lower-back pain due to osteoarthritis and a herniated disc. Her pain level is generally at a five to six on a scale of zero to ten but can be as high as nine after gardening. On such a day, Joan tries a cannabis tincture for the first time and takes three drops. Twenty minutes later, she notices that her pain is about the same. She takes another drop, and 20 minutes later, she finds her pain level has decreased to a four. She takes another drop, and 30 minutes later, her pain level is down to a two. In an effort to eliminate the pain completely, she takes another drop, but 20 minutes later, she notices that her pain level has gone back up to a four. In this scenario, Joan's maximum benefit is reducing her pain level from nine

to two, which she achieved after taking five drops of tincture. That is her sweet spot, and subsequent dosing should be limited to five drops two to three times daily as needed.

The same type of titration can be done with inhalation. Patients typically begin to feel the effects of inhaled cannabis in about 10 minutes. If Joan was using inhalation as her method, she would take one puff and wait 10 minutes to reassess her pain. She would take an additional puff every 10 minutes until her pain was relieved or until she noticed that additional puffs did not help or caused her pain to increase. If it took five puffs to achieve maximum pain relief, then that would be her dose.

Deciding on which type of medicine to use depends on convenience of dosing and which method gives you the most relief. Convenience of dosing is determined by several factors. Do you live in a house or apartment building where the aroma of burning cannabis might be an annoyance to your neighbors? If so, then this can create problems because there is no federal housing protection even if you are severely disabled. Do you have respiratory problems that might be aggravated by smoking or vaporizing? Is your nausea so severe that the smell of a tincture might be overwhelming and inhalation is the only way to calm that feeling? Do you only need to medicate at night, or do you want to be able to dose again during the day at your job? You also must consider that one way of using cannabis might work better at alleviating your symptoms. Whatever method you choose, start with a very small dose and gradually increase it. When starting out, I caution against using anything edible. Edibles are difficult to titrate because the absorption is so unpredictable, and you will have no way of knowing when to expect relief. You may eventually work your way to this method, but do it only after you have some experience with the effects of the plant.

WHEN WILL IT START WORKING, AND HOW LONG WILL IT LAST?

Once inhaled, cannabinoids rapidly enter the bloodstream and cross the blood–brain barrier within minutes. The effects of inhaled cannabis can be appreciated in about 10 minutes. Ingested cannabis yields blood levels that are about 25 to 30 percent of those obtained by inhalation. Because absorption is unpredictable, the effects may not be apparent for hours. While the literature says effects of consumed cannabis may take up to two

hours, patients often report not appreciating the effects for many hours later. Cannabinoids love fat and accumulate in fatty tissue, reaching highest concentrations in four to five days. The rate at which the cannabinoids are distributed to other tissues depends on blood flow. Concentrations in areas that receive high blood flow peak in about 30 to 45 minutes, and areas with less blood flow may not reach peak concentrations for one to two days.

Sublingual Delivery (Onset, Twenty to Thirty Minutes; Duration, Five to Eight Hours)

Tinctures and sprays can be used to deliver cannabis medicine to the area under the tongue, which, like the rest of the mouth, is rich in tiny blood vessels called capillaries. While tinctures are found in all medical cannabis markets, sprays may not be as easy to find. I encourage most of my patients to try sublingual tinctures first. If for some reason medicine cannot go directly under the tongue, then it can be deposited between the lower gum and cheek. In both instances, the medicine is held in place for about two to three minutes to allow for direct absorption of medicine into the bloodstream.

I prefer this method for a few reasons. It's discreet and simple: No muss, no fuss, and no smell. This method is ideal for patients who live in multifamily dwellings or who are not comfortable with other family members knowing of their cannabis use. Another important benefit is that the effectiveness can last five to eight hours. With this, patients can dose in the morning before leaving for school or work and often not require an additional dose until late afternoon, when they get home. This lengthy effectiveness is also helpful for patients who wake up during the night after three or four hours of sleep. It is also easy to adjust the dose. Patients should start with a very low dose and wait to see the effects before adding more. Some patients respond to one drop; others require 100.

Tinctures are extracts that contain the active cannabinoids and terpenes and are typically made with alcohol, glycerin, or oil. People absorb and metabolize cannabis differently, and with cannabis, less is more. It is important to start with very small amounts and to titrate, or gradually increase the dose, until the desired effects are attained. Always start low and go slow!

There are different extraction methods. One type uses solvents, like butane, hexane, or propane, to extract the active compounds from the

plant’s flowers and leaves. Once they are made, these solvents should be removed from the concentrate before using. Another extraction method is by supercritical carbon dioxide, which is used as the solvent to remove the cannabinoids and terpenes. These processes produce a concentrated paste that can be dosed in very tiny amounts smeared on the tongue or mixed in oil for more accurate dosing.

Regardless of the method, any pesticides that are on the plant will be concentrated as well. Using concentrates purchased from anywhere other than a licensed medical dispensary in a state that mandates third-party testing, poses the risk of exposure to high levels of these solvents and pesticides; therefore, never use a tincture that has not been tested for potentially toxic substances. Levels should meet standards established by regulatory boards, which vary from state to state.

Cannabinoids and terpenes can also be extracted by soaking the flower in oil—typically organic olive, canola, safflower, sesame, or a medium-chain triglyceride (MCT) oil. Some patients who grow their own plants make their tinctures by soaking the buds in oil over several days to weeks.

Alcohol is the traditional method for making tinctures and is commonly used because it doesn’t require as much time as oil extraction. After the cannabis flower has been gently stirred or agitated in alcohol for 15 to 20 minutes, the cannabinoid-rich alcohol can be used by the patient, or the alcohol can be allowed to evaporate, leaving a gummy residue that can then be mixed with oil.

Tinctures typically come in amber or dark-blue glass bottles to protect the cannabinoids and terpenes from degradation by UV light. They should be stored in a dark, cool place, like a medicine or kitchen cabinet or bedside drawer. They usually come with an eyedropper top. Before using, one must make sure all of the medicine is in the bottle, that there is no tincture in the eyedropper itself. Gently shake the bottle, draw up the liquid into the eyedropper, and count the drops with the aid of a mirror. If a mirror is not available, the drops can be counted into a spoon and then poured under the tongue. If the tincture is oil based, then the drops can go directly under the tongue. If it is alcohol based, putting the tincture directly under the tongue will be quite uncomfortable, so it’s best to start it on top of tongue and mix with saliva or place the drops in a spoon with a small amount of oil and then place under the tongue. There the tincture rests for two to three minutes to allow the compounds to be absorbed directly into the bloodstream. What is swallowed may be absorbed via the digestive

tract. With gastrointestinal absorption, the rate will vary from patient to patient, and plasma levels are lower than those attained with inhalation. Keep in mind that cannabinoids love fat, not water, so to increase absorption with ingestion, always mix with a fatty substance.

With the under-the-tongue method of delivery, the patient typically begins to feel the medication's effect in about 20 to 30 minutes. If symptoms don't respond after about 20 minutes, then the patient can add a drop and continue to add a drop every 20 minutes until they experience relief. Sprays are another way to deliver medicine sublingually. Patients typically start with one to two sprays under the tongue. Again, it's all about adding to the dose every 20 minutes until you know the amount required based on your body's response. An advantage to using tinctures is that the effects last about five to eight hours. They are typically dosed twice daily but can be used every three to four hours if need be. The exceptions to titrating every 20 minutes are for seizures and psychiatric symptoms. For psychiatric conditions, doses are typically increased every three to four days, and for seizures, once every three weeks.

Once maximum relief is achieved, the patient adds up the number of drops that were needed; the next time they need to medicate, they use that number of drops. One drop equals about 0.04 milliliters. The patient can also convert the number of drops into milliliters and dose with a medication syringe. For example, if your dose is 12 drops, then multiply 12 by 0.04, which yields 0.48, or about 0.5 milliliter. If you know how many milligrams of THC or CBD is in a milliliter of your medicine, then you can calculate how many milligrams you need (see textbox 8.2).

Textbox 8.2 Example of Dose Calculation

Your medicine contains 250 milligrams of THC in a 15-milliliter bottle. If you divide 250 by 15, you get 16.7 milligrams per milliliter. If you require 0.5 milliliter to experience relief, then multiply 0.5 by 16.7, and your dose is 8.4 milligrams, or roughly 8 milligrams of THC. You must keep in mind that the terpenes in the plant also influence how you will respond, so this amount of cannabinoid may not always be required. In a product from a plant with a different cannabinoid and terpene profile, you might require a little more or a little less THC.

While not usually taken sublingually, concentrated pastes are often dosed by smearing a small amount on the tongue—about the size of a grain of

rice. Much of the medicine is absorbed, like the tinctures and sprays, through the blood vessels in the mouth, while the rest is ingested and absorbed through the gastrointestinal tract. Gastrointestinal absorption is less predictable, so it may take more time to determine your dose. Patients who gradually increase the amount of medicine to fight cancer often use this method.

Intranasal (Onset, Fifteen to Thirty Seconds; Duration, Two to Four Hours)

Intranasal spray is not often used, nor is it readily available in all areas, but it is an excellent way of delivering medicine, particularly CBD, quickly and efficiently. It is often formulated for rapid absorption through the fine blood vessels in the nose and is typically used as rescue medication for seizure patients. The onset of action after intranasal delivery can be rapid, often aborting a seizure within 15 to 30 seconds.

Inhalation (Onset, Ten to Fifteen Minutes; Duration, Two to Four Hours)

Inhalation is the form of delivery most commonly associated with cannabis use. It offers the advantage of higher plasma levels and a rapid onset of action. The bioavailability is 2 to 56 percent, depending on technique, as there is significant loss of medication in side-stream smoke. Inhalation is done by smoking or vaporizing the plant itself or as a resin, wax, or concentrate. Patients should take normal breaths when smoking or vaping. The long, drawn-out, one- to two-minute breath holds, which are common practice in recreational circles, are not necessary and do not add to the absorption or ultimate plasma levels.

The medicine is in the bloodstream within seconds, and initial effects occur in minutes. When patients begin using cannabis, they should start with one or two puffs and wait about 15 minutes before adding a puff. While the compounds are in the blood almost immediately, it can take 15 to 30 minutes to feel the maximum effect. Once symptoms are relieved, the number of puffs is added up, and that is the dose for that batch of cannabis product. The amount of time the medicine is in effect with inhalation is anywhere from one to four hours, depending on the individual, but most typically, it is in the two- to three-hour range.

There are a few conditions for which inhalation is the preferred mode of delivery. Patients with migraines or seizures who experience auras or

prodromal symptoms can sometimes prevent an attack by dosing via inhalation. Patients with panic attacks or sudden severe pain or muscle cramps can also benefit from the rapid onset. Inhalation is also great for treating nausea. Patients who have difficulty falling asleep but stay asleep benefit from the rapid onset and can vape or smoke a few puffs at bedtime, which allows them to fall asleep in less time.

Smoking

Some patients prefer smoking to other forms of inhalation. Loose cannabis flower can be rolled into thin cigarettes, called joints; fat, cigar-like cigarettes called blunts; or smoked in a traditional pipe or water pipe, sometimes referred to as a bong. Medical cannabis can also be purchased in cigarettes called prerolls. Interestingly, cannabis has not been associated with an increased risk of lung cancer, abnormal lung function, and COPD to the degree that tobacco smoking is.[3] This may in part be due to the fact that the amount of smoke inhaled is usually less than that of tobacco and that cannabis is both anti-inflammatory and a bronchodilator. Some recent studies show that there is an increased risk of lung cancer in heavy cannabis users.[4] This has not been documented in patients who may only take a few puffs per day, but more longitudinal studies on the long-term effects of smoking cannabis are needed as the use of smoked cannabis increases. However, any form of smoking will expose the patient to products of combustion, which are carcinogenic and have the potential of increasing the risk of other forms of cancer.

Vaping

Vaporizing, or vaping, is very similar to smoking except that the cannabis is heated to a temperature just below combustion, which for cannabis is 392 degrees Fahrenheit. The cannabinoids and terpenes boil and evaporate at various temperatures, and vaporizers can be set to maximize the vaporization of these compounds without exposing the patient to carcinogenic products of combustion. With controlled temperatures, the patient can potentially maximize the effectiveness of their treatment by targeting certain cannabinoids, terpenes, and flavonoids. One drawback to vaping is that the lower temperatures may not be high enough to boil some of the terpenes and flavonoids that have medicinal benefits. Vaping at 410 degrees will ensure that the patient is dosing with most of the compounds but will likely miss THCV, CBC, terpineol, quercitin, and possibly linalool.

The vaporizers vary in size, complexity, and cost and can use either flower or concentrates or both. There are desktop models, portable models that can be carried in a purse or pocket, and small vape pens. Desktop vaporizers are stationary and operate with an inflatable bag that fills up with vaporized cannabis and holds it over an extended period of time. Patients who experience more relief by vaping but require multiple doses per day can fill the bag and dose periodically without having to reload it with cannabis. Most portable vaporizers can be used with either cannabis flower or concentrated vape oil. It is important to note that oil-based tinctures are not the same as oils made for vaping and should not be interchanged. There are also disposable vaporizers that are preloaded with concentrate. They come in pen-like models that can be discarded and in cartridges that can be attached to a vaping pen.

It is important to pay attention to the concentrations of these oils because they are commonly very high. I generally discourage patients from using highly concentrated products because cannabis usually works best at low to moderate doses. A recent study found that vaping low doses of THC (1.29 percent) improved neuropathic pain to greater degree than high doses (3.5 percent) and, based on cognitive testing, was not expected to have an adverse effect on daily functioning, further evidence that cannabis works best at low to moderate doses.[5] High doses of THC also increase the risk of side effects and developing tolerance or dependence. Both smoking and vaping are associated with increased sputum production and cough in some patients.

Nebulizing

Another way of using cannabis is with a nebulizer, which is a small machine or inhaler device commonly used to treat asthma or wheezing attacks. This method delivers medicine to the lungs without the patient having to actively draw a breath as with smoking or vaporizing. The medicine is mixed in saline (saltwater) and reaches the airways by simply breathing through the nose or mouth with a mask or mouthpiece. This delivery system works well for children and patients with asthma or pain who are unable to draw from a vaporizer or whose airways are irritated by the heated vapor. This is also useful if there is a need to inhale cannabinoid acids, like CBDA or THCA.

Dabbing

Heating highly concentrated resins on a small metal head to very high

temperatures is referred to as dabbing. It delivers a whopping dose of cannabinoids. It is the preferred method of delivery for many recreational users because of the high plasma levels of THC and intoxication that can be attained. While this method is touted by some patients with severe pain as the only method that is effective in relieving their discomfort, clinical studies have shown that THC works best for pain at low to moderate doses and at high doses is relatively ineffective at treating pain.

Perhaps there are patients who are rapid metabolizers or who have developed tolerance from prolonged cannabis use at high doses, but generally speaking, I don't see dabbing as a good method for medicinal use. Remember, in Ayurveda, cannabis heals, and it poisons. And while the poison will not kill you, high levels of THC can cause paranoia, nausea, vomiting, confusion, hallucinations, delirium, and long-term problems with memory and cognition and can lead to dependence and tolerance.

Oral (Onset, Forty-Five to Ninety Minutes; Duration, Eight to Ten Hours)

Cannabis is available in capsules and tablets. In my practice, this way of using cannabis seems to be favored by patients with gastrointestinal conditions, like Crohn's disease and ulcerative colitis. Capsules are usually dosed once or twice daily. A starting dose is typically 2.5 milligrams of THC or 10 milligrams of CBD. The dose is gradually increased in increments of 2.5 to 5 milligrams.

Topical (Onset, Five to Ten Minutes; Duration, Eight to Ten Hours)

There are a number of different topical products: salves, creams, gel sticks, lotions, and transdermal patches. Topical application can be used to alleviate both inflammatory and neuropathic pain. It can reduce the pain and swelling of arthritic joints, release muscle spasms, alleviate eczematous rashes and psoriatic plaques, reduce migraine pain, and alleviate acne and the itch from insect bites. I advise patients to apply their topical in thin layers as often as needed until the pain, muscle spasm, or itching subsides. Migraine patients often massage topical salves into the temples, at the base of the skull, and on the back of the neck. Some patients report that this topical application actually aborts the migraine. This is especially helpful when a migraine occurs at school or at work.

THC does not pass through intact skin, so there is no psychoactivity

associated with topical use. However, caution should be exercised if there are cuts or abrasions. Although the amount absorbed should not cause any significant intoxication, it could possibly cause a positive drug screen.

Transdermal patches penetrate deeper and deliver medicine to the bloodstream. They are helpful in delivering a steady dose of medicine over time. I often recommend transdermal patches for patients with seizures, severe anxiety, or severe pain. They can also be useful for preventing nausea and vomiting associated with chemotherapy and for stimulating the appetite over several days. They are also very useful for patients who are unable to cooperate with other delivery modes. The therapeutic effects can last for several days, and intoxicating effects are less of a problem because of the slow delivery of THC.

Edibles (Onset, One to Six Hours; Duration, Eight to Fifteen Hours)

The broad category of edibles includes everything from cooked and baked items to candies, teas, milks, and smoothies. Tinctures, which are usually used under the tongue, are often listed on cannabis menus as edibles because some patients add the drops to food or beverages. Many patients find that sipping on a cannabis tea or eating a chocolate is especially effective for alleviating pain and promoting uninterrupted sleep. There are a few advantages and many disadvantages to using cannabis edibles for medicinal purposes.

When cannabis is swallowed, it goes through the process of digestion, and a substantial amount of medicine is lost. Needing larger amounts of product to achieve therapeutic plasma levels similar to those achieved by inhalation or sublingual makes this the most expensive way to use cannabis. In one study, blood concentrations of THC were found to be 25 to 30 percent of those resulting after smoking the same dose.

Edibles are also the method most associated with overdoses. Because the time it takes to be effective is lengthy and unpredictable, patients often dose and after an hour or two think that they have not taken enough or have forgotten the initial dose and so will dose again. That can be enough to cause adverse effects when the medicine finally kicks in, which can be hours later. While the side effects of too much THC are not deadly, they can be unpleasant and typically consist of nausea and vomiting, dizziness, and paranoia.

That being said, edibles may be the best mode of delivery for some patients with severe pain. As part of the digestive process, the cannabis

goes through what is referred to as the first hepatic pass. As cannabis passes through the liver, the delta-9 THC is converted to 11-OH-THC. This form of THC has more intoxicating effects than the previous form, but it also has a greater pain-relieving effect. For patients with significant pain that is not responding to inhalation or sublingual administration, edibles may be more effective.

When ingesting cannabis, it is important to add a fat. Because the cannabinoids are lipophilic, or fat-loving, the fat will substantially increase absorption. There are now preparations that, through microemulsion technology, are hydrophilic (water-loving), which increases the water solubility of the cannabinoids. This increases gastrointestinal absorption and bioavailability.

Ingesting cannabis does not necessarily require baking brownies. Cannabis butter can be used on toast as well as in a recipe. Cannabis can be steeped in milk or tea and sipped. Chocolates and lozenges have the advantage of lingering in the mouth for a while, which allows for some direct absorption. This will decrease the amount of time it takes to feel the effects. The rest is digested, which extends the amount of time it remains effective.

Intoxication is not a problem for high-CBD varieties, but this first hepatic pass raises the possibility of drug interactions, and caution should be exercised. Dosing CBD too close to certain medications can increase risk of adverse effects for such medications as warfarin, anticholesterol medications like statins, benzodiazepines, antiseizure medications, and tricyclic antidepressants. Another disadvantage to swallowing cannabis is the unpredictable absorption and onset of action. The rate of absorption not only varies from patient to patient but also for the same patient from day to day. Onset of action can be anywhere from 40 minutes to 3 hours.

The duration of action for an edible is much longer than any other mode of delivery. The effects can last anywhere from 8 to 14 hours. This can be a great advantage for patients with chronic pain or difficulty sleeping more than a few hours at a time.

Suppositories (Onset, Ten to Twenty Minutes; Duration, Five to Eight Hours)

Rectal and vaginal suppositories are available in some markets. Some patients find that suppositories offer better pain relief for issues like pelvic pain from menstrual cramps, endometriosis, fibroids, arthritic hip pain, or

pain from colitis. Some patients believe they can absorb THC through the rectum and avoid its intoxicating effects. Patients wishing to take very large quantities of THC to treat cancer particularly misunderstand this. They are not becoming intoxicated because the THC is not being delivered to the bloodstream. Only a synthetically altered THC-hemisuccinate is absorbed through the rectum. THC in its natural state is not, so patients may experience local pain-relieving effects or the effects of the other cannabinoids and terpenes without becoming intoxicated.

OVERDOSE

Cannabis has a very high safety profile, so if you take too much, don't panic. The symptoms from cannabis overdoses last until the medicine wears off, and this depends on how it was taken. With inhalation, your misery lasts about two to three hours; with sublingual delivery, up to 8 hours; with edibles, possibly many more hours. But you will not die. I recommend that, regardless of what kind of medicine you find works best, always keep a CBD tincture or vape pen in the house. In the event that you take too much THC, dose with CBD tincture at 5 to 10 minutes every 20 minutes or 1 to 2 puffs every 10 minutes until you feel better. This is not a guaranteed antidote, but many cannabis users report experiencing relief from the anxiety and nausea that result from taking too much THC.

Deciding on the best dose and delivery system is a process and may take several days or weeks to determine. Comparing the three most common forms of using cannabis, we know the following:

- Inhalation gives the fastest relief, but the effect doesn't last more than two to three hours.
- The absorption of edibles is unpredictable and varies depending on what is in the gut. It takes the longest to take effect, but the effects last 10 to 14 hours. Consuming cannabis with THC increases its pain-relieving properties but also its intoxicating effects.
- Sublingual tinctures take about 20 minutes to start working and usually last 5 to 8 hours.

Patients respond to cannabis differently, so dosing varies from person to person and product to product. Always start with a low dose, and gradually increase it until you experience the maximum benefit. The maximum benefit may mean a reduction in symptoms and not total elimination.

There’s no one-size-fits-all with cannabis medicine. You may find it best to try a variety of methods to see what works best for you in alleviating your symptoms. After a few weeks of treatment, some patients find that they do not need to dose every day to manage their symptoms, but by using the lowest amount necessary to relieve your symptoms, you can stay with that dose for a long time.

Chapter 9

Making Your Own Medicine

The plant was named *Cannabis sativa* by Carl Linnaeus in 1753 and is known to be extremely hardy. It commonly grows abundantly as a weed in any area that is well watered, like drainage ditches. It is an environmental cleaner, meaning that it sucks up pesticides, contaminants, and heavy metals from the soil. It also uses up nutrients in the soil and will crowd out other vegetation if left to its own devices.

The cannabinoids, flavonoids, and terpenes are the medicine in cannabis and are produced in tiny hair-like projections called trichomes, which are found mainly in the flower and to a much lesser extent on the stems and leaves. It's within these glandular structures where the resin is produced. In addition to producing the plant's medicinal compounds, this sticky substance prevents the plant from losing water.

Cannabis is dioecious, meaning that there are distinctly male and female plants. It was once thought that only the females produced the resin, but it is now known that both sexes produce resin, but the female plant produces much more than the male.

GROWING YOUR OWN

I am not a big fan of homegrown medicine and don't encourage patients to grow their own. With a practice full of patients at risk of developing serious infections—children, the elderly, cancer patients on chemotherapy, and patients on immunosuppressive drugs, I want to know that there are no pathogens—bacteria, mold, or toxins—contaminating the plant that can be deadly to patients who are unable to fight off infections. Cannabis grown in facilities that are highly controlled are less likely to have contaminants that might be harmful, especially if inhaled. Many medical cannabis states have instituted mandatory testing by independent laboratories to ensure that the products are safe for use.

Another reason for promoting dispensary medicine is that, unless the patient has their product tested for cannabinoid and terpene profiles, we don't know what it is about that cultivar that is helping or not helping. Even knowing what the plant is supposed to be does not translate into what you actually get. There are so many things that affect the cannabinoid and terpene content. The amount of UV light, temperature, soil pH, what's in the water, whether the leaves are picked from the top or bottom—all translate into varying concentrations of cannabinoids.

Collectives

In states where growing your own cannabis is allowed, there may be collectives or growing clubs that can help a patient grow small batches of up to five or six plants, depending on the number of plants the state allows the patient to grow. They can assist by helping a patient create a clean and healthy environment in the home for growing and often have access to an accredited lab for testing the end product. This may be the ideal solution for patients who enjoy horticulture and need a more economical source for quality medicine. With some collectives, each patient grows a small amount, so if there is a problem with mold or bacteria, there are only a few plants that have to be discarded. The harvests are tested and then shared among the participants.

Cultivation

Cannabis can be grown indoors or outdoors and in soil or in solutions. Hydroponics is a method of growing plants in mineral nutrient solutions without soil. It is not an easy undertaking, and you have to know which cultivars to grow and which nutrients to use and use the correct water-nutrient solution. If the right nutrients are used, these plants tend to be healthier and produce more medicine.

When it comes to advice on cultivating, though, Eric Jones, chief grower at Holistic Industries, recommends the following:

1. Keep it simple. You don't need an expensive setup to grow high-quality medicine.
2. Research strains online at sites like www.Leafly.com. Find cultivars that meet your needs, and order seeds from a reputable seed bank. Avoid growing from cloned plants, as they may harbor pests and diseases.
3. Grow in organic potting mix in an area indoors where you can control

the lighting 24 hours a day or outdoors from late spring to fall. A commercial growing tent can be used indoors if you do not have a suitable location.
4. Only use organic soil amendments and pesticides. Do not use systemic pesticides—pesticides that do not remain on the surface but are absorbed by the plant. Read the labels thoroughly, and only use through the first four weeks of the flower cycle or up to the day of harvest if approved by the manufacturer for edible crops.
5. Keep things clean and sterile. Wash all equipment and the growing space, if indoors, regularly.
6. Purchase a guide, such as *Indoor Marijuana Horticulture: The Indoor Bible* by Jorge Cervantes.
7. Hydroponic shop employees can provide great advice, but don't let them sell you on "miracle" products.
8. Rinse your plants with plain water and allow them to dry prior to harvest. This will help remove dust and residual contact pesticides.
9. Dry the final flower and leaf product completely over a week to avoid postharvest fungi.

Dry flower and leaves can be smoked or vaporized, or they can be processed into a tincture for sublingual administration. Tinctures are typically alcohol based but can be made into oils, which are easier to administer because they can go directly under the tongue without discomfort. Leaves and stems can be used to make topical salves.

MAKING TINCTURES

Tinctures are relatively easy to make and easy to dose if you know the concentration of delta-9 THC and CBD in your plant material. For THC and CBD tinctures, you must decarboxylate your flower by baking it first. For THCA and CBDA tinctures, skip the baking. There are many opinions regarding the optimal temperature and time for maximum decarboxylation, and I invite you to do your research and experiment. If you live in an area that offers laboratory testing, by all means, do your calculations, but confirm by spending a little extra money to have your tincture tested for its cannabinoid content. If testing for cannabinoids is available, you can gain some really valuable information. Set aside a time when you are not rushed, and prepare a clean work surface, like your kitchen counter or table. You need some basic equipment:

- Scale
- Pyrex dish
- Aluminum foil
- Blender, food processor, coffee grinder, or cannabis grinder
- Beaker or glass bowl with spout
- Funnel
- Strainer
- Cheesecloth or coffee filter
- Jar or Erlenmeyer flask
- Magnetic stirrer or Sonicator for speeding up the process (optional)
- Water distiller (optional)
- Amber or blue tincture bottles with eyedropper tops
- Everclear grain alcohol
- MCT or organic olive oil

1. Weigh your flower. It is more economical to use shake (broken pieces of flower, not the intact bud). If you are using dispensary medicine, then you can skip this step, as the weight is on the package.
2. Do your calculations. Multiply the weight of the flower by the concentration of cannabinoid. For example, if you have 10 grams of flower that is 15 percent CBD and 18 percent THC, then multiply:

   10g × 0.15 = 1.5 g × 1,000 = 1,500 mg CBD
   10g × 0.18 = 1.8 g × 1,000 = 1,800 mg THC

   You lose approximately 20 percent during the process, so you must multiply your totals by 0.8:

   1,500 mg × 0.8 = 1,200 mg CBD
   1,800 mg × 0.8 = 1,440 mg THC

3. Place the flower in a single layer in a rimmed cookie sheet or Pyrex dish, cover with foil, and heat at 240 degrees F for 45 to 60 minutes, or 250 degrees F for 25 minutes, stirring every 10 minutes to ensure even heating. This converts, or decarboxylates, the THCA to THC. Keep covered and allow to cool completely. The flower should be dry and crumbly, not scorched or crispy.
4. Once the flower is cool, grind it to increase the surface area that comes into contact with your solvent. Don’t overgrind. You don’t need

powder.

5. Place the ground flower into a beaker or glass bowl and add grain alcohol, enough to cover the flower completely.
6. Place in a Sonicator or magnetic stirring plate. If using a magnetic stirrer, you must place a magnet in the beaker as well. Turn it on for 15 to 20 minutes, until the solution is dark green. (If you do not have this type of equipment, then you can place the flower and alcohol in a jar and shake a couple of times a day for 7 to 14 days.)
7. Strain the liquid through a kitchen sieve to remove the larger plant material; then strain again through a funnel lined with either cheesecloth or a coffee filter to remove the finer sediment and particles.
8. At this stage, you have an alcohol tincture that you can use for medicine. If you plan to take your medicine under the tongue, then you don't want to use an alcohol tincture because it is very harsh and stings. Oil is also preferred for tinctures for children. Some patients are very sensitive to alcohol and want to avoid even these very small doses.

   To make an oil-based tincture, pour your liquid into a water distiller to extract the alcohol. This leaves a gummy substance that contains all of the cannabinoids and terpenes. Transfer the substance to a clean jar. Add organic olive oil or MCT oil to complete the process, and mix thoroughly.

   For making a THCA and CBDA tincture, you want to skip the baking and the water distiller. The distiller gets hot and may convert some of your acid cannabinoids into THC and CBD. Instead, pour the liquid onto a flat pan, and allow the alcohol to evaporate. Placing a fan nearby speeds up the process. When the alcohol has evaporated, scrape the resin from the pan, gradually adding your oil to loosen it. Once it's a consistency that can be scooped or poured, transfer it to a measuring cup or beaker and add your MCT oil or olive oil; then pour it into an amber or cobalt blue tincture bottle, and store in a dark, cool place.

   Next, you have to decide how concentrated you want your tincture to be. Take the total number of milligrams and divide by the number of milligrams you want per milliliter. For example, if your batch contains 1,440 milligrams of THC and you want your tincture to have 10 milligrams per milliliter, then your calculation would look like this: 1,440 mg ÷ 10 mg/mL = 144 mL. If you want your tincture to have 5 milligrams per milliliter, then add 288 milliliters of oil. If you have 1,200 milligrams of cannabinoid and want to make a tincture with 10

milligrams per milliliter, then add 120 milliliters of oil.

While I am not an expert at making tinctures, I have made THCA and CBDA tinctures because they are generally not available in my geographical location. Using the methods here results in concentrations of THCA and CBDA that have been remarkably close to my calculations. If, however, this is too labor intensive, then try making tinctures with an herbal infuser, like the Magical Butter Machine or Mighty Fast Herbal Infuser, sold online and in many dispensaries. These machines can be purchased for around $175.

MAKING EDIBLES

Edibles are difficult to dose because of their unpredictable absorption, and they are easy to overdose on because patients often think they haven't taken enough. They can be useful for patients with pain that does not respond to other forms of cannabis because the pain-relieving effect is increased. Care must be taken with edibles because the intoxicating effect of the THC is also enhanced. Ingestion increases the pain-relieving effects by converting delta-9 THC to 11-OH-THC. This compound not only has superior pain-relieving effects, but it is also more intoxicating than delta-9 THC, which does not make it practical for daytime use in patients who are working, in school, or driving.

For patients who wake up frequently in the night, edibles can be helpful because the effect lasts longer than any other mode of delivery: 8 to 10 hours and sometimes longer. If you are in need of increased pain relief or prolonged effectiveness, chocolates are a good choice. The chocolate lingers in the mouth for a while, so some medicine is absorbed there. Also, the fat in chocolate will increase the absorption in the intestines.

Melt chocolate chips and thoroughly mix in your concentrate. Pour the mixture into a shallow pan or mold and score into the appropriate number of pieces. If you have 500 milligrams of THC and want each chocolate serving to have 5 milligrams, then you will have 100 pieces. Even with thorough mixing, chances are the medicine will not be evenly distributed, so you will run the risk of having a chocolate that has more or less than the dose you want.

Cannabis/Turmeric Latte

This is a recipe for a creamy, savory, yet sweet latte made with

inflammation-fighting cannabis, turmeric, coconut milk, almond milk, and MCT oil. This is very simplified version of a traditional Bhang Lassi drink served in India and Nepal during Hindu festivals like Holi, Janmashtami, and Shivratri. The original recipe calls for yogurt, nuts, spices, and rosewater. The fat in the recipe increases the absorption of the cannabinoids, and fat and black pepper (piperine) enhance the bioavailability of curcumin, the active anti-inflammatory compound in turmeric. It's best to sip these concoctions slowly so that you are relaxed and not overwhelmed by too much of an intoxicating effect.

Native to southern Asia, turmeric is a relative of the ginger plant. It has also been used for thousands of years in Ayurvedic medicine. Studies show that turmeric contains compounds that block the formation of amyloid proteins, the hallmark of Alzheimer's disease, and dozens of anti-inflammatory compounds, including curcumin. It has been shown in animal studies to be effective in treating certain cancers. Many of my patients with chronic pain experience relief with this simple concoction. Organic, fresh-ground turmeric is best. If adding cannabis, use a variety with a CBD:THC ratio of 1:1 for daytime pain relief. If pain is persistent, try increasing the THC gradually. For insomnia or nighttime pain, sip a THC-rich variety high in myrcene an hour before bedtime for a restful, restorative, pain-free night. For patients in nonlegal states, follow this recipe without the cannabis oil or, if allowed in your state, with hemp-derived CBD.

2.5–10 mg cannabis concentrate (for cannabis-naïve patients, start with 2.5 mg; you can gradually increase the potency by 2.5-mg increments until it is effective in relieving your pain, muscle spasm, or insomnia)
1 T MCT oil
½ c. full-fat canned coconut milk (or you can use 1 T grass-fed butter or ghee if you eat dairy)
c. almond milk
½ t ground turmeric
½ t vanilla extract
1 T honey
Pinch of sea salt
Pinch of ground cinnamon
Pinch of black pepper

Add all ingredients to a small saucepan. Stir and simmer over low heat for about two minutes. Pour into your favorite mug, and sip slowly.

Cannabis Milk

Use a cannabis variety with a CBD:THC ratio of 1:1 for daytime pain relief. If pain is persistent, try increasing the THC gradually. For insomnia or nighttime pain, use a THC-rich variety high in myrcene an hour before bedtime for a restful, restorative, pain-free night.

1g of ground cannabis flower CBD:THC ratio 1:1
2c. prepared or homemade almond milk (or coconut milk or whole grass-fed milk)
⅔ t coconut oil (or grass-fed butter)
Pinch of nutmeg or cinnamon
Honey to taste

Stir occasionally over low heat.

Chapter 10

Hemp-Derived Cannabidiol (CBD)

Many patients and families who live in states without legal access to medical cannabis rely on CBD oil to treat a number of conditions, the most common being intractable seizures in children.

CBD derived from hemp is the same molecule as CBD from the marijuana plant. CBD has antiseizure, antianxiety, anti-inflammatory, antispasmodic, antinausea, gastrocytoprotective, neuroprotective, antitumor, mood-stabilizing, antipsychotic, and antioxidant benefits. It has been shown in several studies to alleviate neuropathic as well as inflammatory pain.[1] It modulates the autoimmune system and regulates glucose and fat metabolism.[2] It is especially effective in alleviating visceral pain, decreasing gastrointestinal inflammation, and regulating gastrointestinal motility. It is an appetite suppressant and can be energizing at low doses. CBD is known to protect the heart muscle from ischemic damage and oxidative stress.[3]

While it has been found to have antidepressant activity in animal studies, care must be given when using CBD-rich varieties without THC in depressed patients who are not being treated with antidepressants.[4] In my clinical experience, these patients sometimes experience a worsening of their depressed mood when CBD is used all by itself. In this situation, it's best to use a CBD tincture or oil that has a higher delta-9 THC content than 20:1. I typically recommend a ratio between 5:1 and 10:1.

CBDA is extracted from the raw hemp plant before heating. This nonintoxicating cannabinoid also has antitumor and anti-inflammatory properties. Part of its anti-inflammatory effect is due to the inhibition of an enzyme called cyclooxygenase-2 (COX-2). This enzyme is needed to convert arachidonic acid into prostaglandins, which are proinflammatory mediators. CBDA, like CBD, also increases the body's endocannabinoid anandamide levels. Unlike medications that are COX-2 inhibitors, CBDA

is not toxic to the heart or kidneys. Extracts with both CBD and CBDA can be very effective, especially for patients with inflammatory bowel disease, arthritic pain, and other forms of inflammation.[5]

I am not an attorney and am in no way trying to give legal advice, but there is a great deal of controversy regarding the legal use of the nonintoxicating cannabinoid CBD. The DEA declared all components in the marijuana plant, including the nonintoxicating molecules, to be Schedule I—of no medical benefit and highly addictive, neither of which apply to CBD. However, title 7, section 5940, of the 2014 Farm Bill (Legitimacy of Industrial Hemp Research) defines industrial hemp —*Cannabis sativa* L. (and all of its parts, whether growing or not, and containing less than 0.3 percent THC)—as a plant distinct from marijuana. Marijuana is sometimes also referred to as the "drug-type" plant versus "fiber-type" plant, which is the industrial hemp. More than half of the United States allow for the production of hemp, and the list is growing, as additional states introduce legislation to make it legal to cultivate, process, and market under the provisions of the bill. They include Arizona, California, Colorado, Connecticut, Delaware, Florida, Hawaii, Illinois, Indiana, Kentucky, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Mexico, New York, North Carolina, North Dakota, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Utah, Vermont, Virginia, Washington, and West Virginia. The hemp must be grown for approved agricultural pilot programs or research. Programs must study the growth, cultivation, or marketing of industrial hemp, so the sales and marketing of hemp materials is allowed. This is why hemp-derived CBD oil is readily available online and in many vape stores and health-food stores.

There are many reputable brands of hemp-derived CBD on the market; however, there are some that are not what they say they are. The processing of these oils, as with other nutraceuticals, is not well regulated, and some unscrupulous businesses sell oils that don't have the potency they claim or may use plant materials contaminated with pesticides, toxins, solvents, or heavy metals. It is important to research the brand and, if need be, to send a sample to an accredited laboratory for testing before using or administering to your child. A recent study published in the *Journal of the American Medical Association* tested for labeling accuracy 84 CBD products purchased online from 31 companies. CBD concentrations ranged from 0.01 milligrams per milliliter to 655 milligrams milliliter, with

labeled concentrations ranging from 1.33 milligrams per milliliter to 800 milligrams per milliliter. Products were underlabeled for CBD 42.85 percent of the time; 26.19 percent were overlabeled; only 30.95 percent were labeled accurately. Vape oils were most often mislabeled, with 87.5 percent (21 of 24 pens) having inaccurate information. Forty-five percent of the hemp oils were accurately labeled. Interestingly, THC concentrations were elevated in eight of the samples, with concentrations as high as 6.43 milligrams per milliliter.[6]

As of January 2018, Kansas, who has been unable to get medical cannabis or even low-THC oil passed, is attempting to pass legislation to allow hemp cultivation under the 2014 Farm Bill. Should they succeed, patients would be able to use hemp oil as a source of CBD. Idaho, another state with no medical cannabis, unfortunately, is not on the list. This means that using hemp-based products like Charlotte's Web and Palmetto Harmony, both CBD oil derived from industrial hemp available online, may not be legal to use in those states.

Though *Cannabis sativa*, or marijuana drug-type plants that are used to extract CBD for dispensaries, may have a richer terpene profile, hemp-derived CBD oils can also be very effective. While some advocates view CBD as less than ideal, it may actually have the most medical benefits. Another argument against CBD derived from hemp is the inferior terpene profile that is associated with the more fibrous form of the cannabis plant. Though having both cannabinoids work synergistically may be ideal, in less-than-ideal circumstances, CBD can be of great benefit to many patients. I have seen remarkable results in patients using hemp-derived CBD to treat gastrointestinal inflammation, arthritic pain, Lyme disease, anxiety, psychosis, neuropathic pain, nausea and vomiting, myasthenia gravis, and lupus.

Seven hemp-producing states do not have medical cannabis laws that allow access to cannabis with greater than 0.3 percent THC. It is, however, legal for patients in these seven states to use hemp-derived CBD oils. If medical cannabis is out of reach because of where you live, but you live in a state where it is legal to purchase hemp-derived CBD, then it can be used to alleviate many of the symptoms that respond to cannabis.

Chapter 11

Self-Care

Toning Your Endocannabinoid System

Our endocannabinoid system (ECS) exists to create balance or homeostasis, and it has the inherent capacity to regulate and heal. Abnormal endocannabinoid signaling has been implicated in the pathophysiology of various medical conditions, including autism and Alzheimer's disease. Migraines, fibromyalgia, PTSD, chronic anxiety, irritable bowel syndrome, and Parkinson's disease are thought to be part of a state of downregulation called endocannabinoid deficiency syndrome, as described by Ethan Russo.[1] An overactive or upregulated ECS, described by Vincent Di Marzo and colleagues, has been linked to obesity, abnormal glucose metabolism leading to type 2 diabetes, and elevated triglycerides and LDL cholesterol.[2] When patients suffer from conditions like chronic pain, seizures, and autoimmune and neurodegenerative diseases, it appears that augmenting our endocannabinoids with cannabinoids from the plant alleviates a multitude of symptoms.

The endocannabinoids our bodies produce, anandamide and 2-AG, are derived from arachidonic acid, a polyunsaturated omega-6 fatty acid. These endocannabinoids are not stored in vesicles but are made on demand and in small amounts. Once they are released from the receptor, they are destroyed by hydrolyzing enzymes FAAH and MAGL. By activating cannabinoid receptors, they are able to modulate appetite, mood, pain, inflammation, seizure activity, anxiety, spasticity, sleep, fat and glucose metabolism, gut motility, gastric acidity, and bone formation. Cannabinoids prevent cartilage destruction and decrease allergic inflammation. They have been shown in animal studies to protect neurons and the cells lining the gastrointestinal tract, and it is clinically apparent that cannabinoids offer protection to brain cells and heart muscle.

It has been shown that our ECS can be enhanced through healthy lifestyle changes that include healthy food choices and exercise, dietary supplementation with omega-3 fatty acids and *Lactobacillus*, stress reduction, and exercise. These measures are beneficial for everyone, but

they are especially important for people suffering from symptoms associated with either an upregulated or downregulated ECS—chronic pain, metabolic syndrome, depression, anxiety, and mood disorders.

NICOTINE

Smoking tobacco not only increases your risk for cancer and respiratory and cardiovascular disease, but it also fuels your pain. Nicotine, like sugar, increases levels of proinflammatory mediators that increase inflammation and pain. If you want to diminish your pain, you must stop smoking tobacco. That advice extends to the use of e-cigarettes as well.

DIET

The standard American diet (SAD) is pro-inflammatory. High in sugar and omega-6 fatty acids, it contributes to the release of pro-inflammatory mediators and endocannabinoid hyperactivity. While some omega-6 is necessary for the production of anandamide and 2-AG, excessive levels can lead to an overactive ECS, which stimulates appetite and increases the risk of obesity, diabetes, and hyperlipidemia, also known as metabolic syndrome.[3]

Scientists have determined that the ideal ratio of omega-6 fatty acids to omega-3 fatty acids is no more than 4:1. In the SAD, the ratio is closer to 16:1. The 4:1 ratio has been shown to decrease mortality from cardiovascular disease by 70 percent! A 2:1 to 3:1 ratio reduction decreased inflammation in patients with rheumatoid arthritis.[4]

Processed foods—stripped of their natural anti-inflammatory and antitumor terpenes and flavonoids—take the place of terpene- and flavonoid-rich fresh fruits and vegetables. Factory-farmed animals living in crowded, inhumane conditions are laden with stress hormones when they land on our dinner plates. Certain pesticides have been found to disrupt normal endocannabinoid signaling, so just increasing conventional fresh fruits and vegetables (laden with pesticide residue) may not be enough.[5] Busy, overcommitted families and individuals dash from place to place, grabbing a bite and mindlessly gobbling highly caloric food, which leads to excessive calorie intake, weight gain, and obesity. We are literally eating ourselves sick.

While exercise is important for maintaining good health for everyone, for patients with chronic pain and metabolic syndrome, it’s especially

important. Medium- to high-intensity exercise burns calories, increases metabolism, improves cardiac function and muscle tone, strengthens bones, and increases anandamide levels (but not 2-AG). Chronic-pain patients need to keep things moving. Being sedentary makes pain worse. Find something you can do within your physical limitations. Walking, chair yoga, tai chi, qi gong, and water aerobics are some of the activities most patients, even with back or extremity pain or weakness, can participate in.

Chronic stress leads to elevated cortisol, which interferes with glucose metabolism and causes elevations in blood sugar, as well as weight gain, fatigue, and sleep disturbances. And as you might have guessed, stress downregulates the ECS. Activities known to reduce the stress response include maintaining healthy social relationships and exercise. Yoga is great for stress relief and stretching as well.

Other methods of upregulating your ECS include acupuncture, osteopathic manipulation therapy, and therapeutic massage. It has been shown in animal studies that electroacupuncture increases anandamide levels in rats.[6] It has been found that anandamide and 2-AG levels do not increase with osteopathic manipulation therapy (OMT) in patients with lower-back pain. In asymptomatic patients, this practice of stretching and applying light pressure to joints and muscles has been found to increase levels of anandamide in other compounds, like N-palmitoylethanolamine (PEA), another endocannabinoid that acts synergistically with anandamide in reducing pain.[7] Therapeutic massage has been shown to increase anandamide levels but not 2-AG.[8]

Knowledge is power. Understanding how all these factors influence your ECS, either positively or negatively, and how diet, stress, and activity increase inflammation and prevents you from being well empowers you to make crucial decisions as they pertain to lifestyle choices. Use your power and your knowledge in your journey to feeling better.

SUGGESTIONS FOR ENHANCING YOUR ENDOCANNABINOID TONE AND DECREASING INFLAMMATION

1. Decrease your omega-6:omega-3 ratio:

    • Algae or wild coldwater fish

- Fatty acids DHA and EPA: 1,000 milligrams of each per day
- Hemp seeds, an excellent source of omega-3 and protein that can be added to salads, yogurt, and vegetables
- Extra-virgin olive oil for no to low heat and avocado oil for high heat
- Eliminate vegetable, sunflower, safflower, and canola oils

2. Adopt a plant-dominated diet by increasing your intake of fruits and vegetables to 9 to 10 servings per day:

    - Strive for fruits like blueberries, blackberries, raspberries, apples with skin, and citrus. Eat vegetables with every meal and from all groups: bulbs (onions, leeks, garlic); flowers (broccoli, cauliflower); green, leafy vegetables (collards, Swiss chard, spinach, watercress, kale); buds (artichokes, Brussels sprouts); roots (squash, carrots, rutabaga, turnips); and tubers (sweet potatoes).
    - Buy and eat organic whenever possible.
    - Eat the fruit, not the juice.
    - Lightly sauté and steam your vegetables to maximize digestibility without destroying nutrients.

3. Reduce natural sugars, and eliminate refined sugar.

    - Refined: table sugar, white flour, pasta
    - Natural: honey, syrup, fruit juice

4. If you eat animal protein, stay with local, pasture-raised eggs and meat.
5. If you are overweight (elevated BMI), lose weight! A 10 percent decrease in body weight can correlate with as much as a 50 percent decrease in pain levels.
6. Supplement with herbs:

    - Black pepper is rich in beta-caryophyllene and binds to CB2 receptors.
    - Ginger, 200 to 2,000 milligrams per day, reduces inflammation.
    - Turmeric (curcumin) increases endocannabinoid levels in the brain, and 1,500 to 2,000 milligrams per day reduces inflammation. Take with fat and black pepper for increased absorption and bioavailability.

7. Stop using nicotine. While it may upregulate the ECS, the increase in inflammation negates any possible benefit in terms of pain relief.
8. Limit alcohol:

    • Small amounts may enhance the ECS.
    • Chronic and binge drinking downregulates the ECS.

9. Incorporate aerobic exercise as tolerated and at your level for 30 minutes a day, 3 to 5 days per week:

    • Walking or running
    • Hydroaerobics
    • Tai chi, qi gong

10. Reduce stress with daily yoga or mediation.
11. Incorporate mind and body treatments:

    • Osteopathic manipulation therapy
    • Acupuncture
    • Therapeutic massage
    • Biofeedback
    • Cognitive behavioral therapy

12. Sleep six to eight hours at night:

    • Bed is for sleep or sex. No watching television or reading.
    • Select a bedtime and stick to it.
    • Create a space that’s uncluttered, dark, and quiet.
    • Clear your bedroom of electronics.
    • Try using a diffuser with drops of lavender oil at your bedside.

Appendix

Lists of Drugs by Metabolism[1]

DRUGS METABOLIZED BY CYP3A4

Abiraterone
Alfentanil
Alfuzosin
Aliskiren
Almotriptan
Alprazolam
Amitriptyline
Amiodarone
Amlodipine
Amprenavir
Aprepitant
Aripiprazole
Astemizole
Atazanavir
Atorvastatin
Bepridil
Bexarotene
Boceprevir
Bromocriptine
Budesonide
Buprenorphine
Buspirone
Cafergot
Caffeine
Cannabinoids

Carbamazepine
CBD
Cerivastatin
Cevimeline
Chlordiazepoxide
Cilostazol
Cinacalcet
Citalopram
Clarithromycin
Clindamycin
Clomipramine
Clonazepam
Clopidogrel
Clorazepate
Clozapine
Cocaine
Codeine
Colchicine
Cyclophosphamide
Cyclosporine
Dapsone
Darifenacin
Darunavir
Delavirdine
Desogestrel
Dextromethorphan
Diazepam
Dihdroergotamine
Disopyramide
Diltiazem
Docetaxel
Dofetilide
Dolasetron
Domperidone
Donepezil
Doxorubicin
Dronabinol
Dutasteride

Efavirenz
Eplerenone
Ergotamine
Erlotinib
Erythromycin
Esomeprazole
Eszoplicone
Ethinylestradiol
Ethosuximide
Etonogestrel
Etoposide
Everolimus
Exemestane
Felodipine
Fentanyl
Fexofenadine
Finasteride
Flurazepam
Flutamide
Fluticasone
Galantamine
Haloperidol
Hydrocodone
Iloperidone
Imatinib
Imipramine
Indinavir
Irinotecan
Isradipine
Itraconazole
Ketamine
Ketoconazole
Lansoprazole
Lercanidipine
Letrozole
Lidocaine
Lopinavir
Loratadine

Lovastatin
Methadone
Midazolam
Mifepristone
Mirtazapine
Modafinil
Mometasone
Montelukast
Nateglinide
Nelfinavir
Nevirapine
Nicardipine
Nifedipine
Nisoldipine
Nitrendipine
Norethindrone
Ondansetron
Omeprazole
Oxybutynin
Oxycodone
Paclitaxel
Pantoprazole
Pioglitazone
Propafenone
Propranolol
Quetiapine
Quinidine
Quinine
Rabeprazole
Ramelteon
Ranitidine
Ranolazine
Repaglinide
Rifampin
Rifaximin
Ritonavir
Rivaroxaban
Rofulmilast

Salmeterol
Saquinavir
Saxagliptin
Sertraline
Sibutramine
Sildenafil
Simvastatin
Sirolimus
Solifenacin
Sorafenib
Sufentanil
Sunitinib
Steroids
Tacrolimus
Tadalafil
Tamoxifen
Telaprevir
Telithromycin
Temazepam
Temsirolimus
THC
Theophylline
Tiagabine
Ticagrelor
Tinidazole
Tipranavir
Tolterodine
Toremifene
Tramadol
Trazadone
Triazolam
Trimetrexate
Valdecoxib
Valproic acid
Vardenafil
Verapamil
Vinblastine
Vincristine

Voriconazole
Warfarin (r)
Zaleplon
Zileuton
Ziprasidone

DRUGS METABOLIZED BY CYP2C9

Amitriptyline
Carvedilol
Celecoxib
Chloramphenicol
Chlorpheniramine
Clomipramine
Clopidogrel
Desogstrel
Diclofenac
Dronabinol
Febuxostat
Fluoxetine
Flurbiprofen
Fluvastatin
Formoterol
Glibenclamide
Glimepiride
Glipizide
Hexobarbital
Ibuprofen
Imipramine
Indomethacin
Irbesartan
Irinotecan
Ketamine
Lomoxicam
Losartan
Mefenamic acid
Meloxicam
Mephenytoin

Montelukast
Nateglinide
Omeprazole
Phenylbutazone
Piroxicam
Quetiapine
Rosiglitazone
Sertraline
Sildenafil
Sulfamethoxazole
Sulfinpyrazone
Suprofen
Tamoxifen
Testosterone
THC
Tienilic acid
Tolbutamide
Torsemide
Valdecoxib
Valsartan
Vardenafil
Voriconazole
Warfarin (s)
Zafirlukast
Zileuton

DRUGS METABOLIZED BY CYP2C19

Amitriptyline
Carisoprodol
CBD
Cilostazol
Citalopram
Clomipramine
Clopidogrel
Cyclophosphamide
Desipramine
Diazepam

Escitalopram
Esomeprazole
Formoterol
Hexobarbital
Imipramine
Indomethacin
Lacosamide
Lansoprazole
Loratidine
Mephenytoin
Mephobarbital
Milutamide
Moclobemide
Nelfinavir
Notripytline
Omeprazole
Pantoprazole
Pentamidine
Phenobarbital
Phenytoin
Progesterone
Proguanil
Propranolol
Rabeprazole
Ranitidine
Sertraline
Teniposide
Thioridazine
Tolbutamide
Voriconazole
Warfarin (r)

DRUGS LARGELY METABOLIZED BY 3A4, 2C9, AND 2C19

Amitriptyline (Elavil)
Clopidogrel (Plavix)
Diazepam (Valium)

Esomeprazole (Nexium)
Imipramine (Tofranil)
Omeprazole (Prilosec)
Sertraline (Zoloft)
Warfarin (Coumadin)

DRUGS METABOLIZED BY BOTH 3A4 AND 2C9

Dronabinol (Marinol)
Ketamine (Ketalar)
Montelukast (Singulair)
Nateglinide (Starlix)
Quetiapine (Seroquel)
Sildenafil (Viagra)
Tamoxifen
THC
Valdecoxib (Bextra)

DRUGS METABOLIZED BY BOTH 3A4 AND 2C19

CBD
Citalopram (Celexa)
Clomipramine (Anafranil)
Lansoprazole (Prevacid)
Pantoprazole (Protonix)
Propranolol (Inderal)
Rabeprazole(Aciphex)
Ranitidine (Zantac)

3A4 INHIBITORS

Boceprevir
Clarithromycin
Cyclosporin
Erythromycin
Itraconazole
Ketoconazole

Verapamil
Voriconazole

2C9 INHIBITORS

Amiodarone
Cimetidine
Cotrimoxazole
Fluconazole
Fluoxetine
Fluvoxamine
Metronidazole
Voriconazole

3A4 INDUCER

Rifampin

Notes

CHAPTER 1

1. A. Snir, D. Nadel, I. Groman-Yaroslavski, et al., "The Origin of Cultivation and Proto-Weeds, Long before Neolithic Farming," *PLOS One* 10, no. 7 (July 2015): e0131422, https://doi.org/10.1371/journal.pone.0131422; P. S. Ungar, *Evolution's Bite: A Story of Teeth, Diet, and Human Origins* (Princeton, NJ: Princeton University Press, 2017), 176–82.

2. E. L. Abel, "Cannabis in the Ancient World," in *Marihuana: The First Twelve Thousand Years* (New York City: Plenum, 1980).

3. H. L. Li, "An Archaeological and Historical Account of Cannabis in China," *Economic Botany* 28, no. 4 (1973): 444; M. Booth, *Cannabis: A History* (New York: St. Martin's Press, 2003.

4. A. Liesowska, "Iconic 2,500-Year-Old Siberian Princess 'Died from Breast Cancer,' Reveals MRI Scan," *Siberian Times*, October 14, 2014; N. Polosmak and C. O'Rear, "A Mummy Unearthed from the Pastures of Heaven," *National Geographic* (October 1994): 80–103.

5. A. A. al-Husayn ibn Sina, *The Canon of Medicine* (1025).

6. E. Tosch, "Ayurvedic Cannabis? Does Marijuana Have a Place in Ayurveda," April 27, 2016, http://everydayayurveda.org/ayurvedic-cannabis.

7. Nadkarni, A. K., *Indian Materia Medica*, with Ayarvedic, Unani-Tibbi, Siddha, Allopathic, Homeopathic, Naturopathic & Home Remedies. Vol. 1 (Popular Book Depot Bombay 7 Dmootapapeshwar Prakaashan Ltd. Panvel, 1941).

8. W. B. O'Shaughnessy, "On the Preparations of the Indian Hemp, or Gunjah," *Provencial Medical Journal* (February 1843).

9. Center for Substance Abuse Research, "Heroin," October 29, 2013, http://www.cesar.umd.edu/cesar/drugs/heroin.asp.

10. Federal Food and Drugs Act of 1906 (The "Wiley Act"), https://prescriptiondrugs.procon.org/sourcefiles/FEDERAL_FOOD_AND_DRUGS_ACT_1906.p

11. Web Guides, "Primary Documents in American History: 18th Amendment to the U.S. Constitution (Prohibition)," October 30, 2017, https://www.loc.gov/rr/program/bib/ourdocs/18thamendment.html.

12. The song "La Cucaracha" was popular with the Mexican soldiers; its chorus references a cockroach that has difficulty coping because he doesn't have marijuana to smoke:La cucaracha, la cucaracha,Ya no puede caminarPorque no puede, porque se faltaMarihuana que fumar.The popular term for the last part of a marijuana cigarette, *roach*, came from this song.

13. D. McDonald, "The Racist Roots of Marijuana Prohibition," *Foundation for Economic Education*, April 11, 2017, https://fee.org/articles/the-racist-roots-of-marijuana-prohibition.

14. "Legislative Ground Sluice from Last Chance Gulch," *Montana Standard* (Butte, MT), January 27, 1929.

15. C. Adams, "The Man behind the Marijuana Ban for All the Wrong Reasons," *CBS News*,

November 17, 2016, https://www.cbsnews.com/news/harry-anslinger-the-man-behind-the-marijuana-ban.

16. "Marihuana Makes Fiends of Boys in 30 Days: Hasheesh Goads Users to Blood-Lust," *San Francisco Examiner*, January 31, 1923, http://www.druglibrary.org/mags/examiner23.htm.

17. A. Halperin, "Marijuana: Is It Time to Stop Using a Word with Racist Roots?" *Guardian*, January 29, 2018, https://www.theguardian.com/society/2018/jan/29/marijuana-name-cannabis-racism.

18. C. E. Hughes, "Jazz Weed Source of Much Crime in the Southwest," *New Castle News*, October 18, 1921.

19. P. Harrison, "In New York," *Shamokin News-Dispatch*, March 28, 1934.

20. P. Gahlinger, *Illegal Drugs: A Complete Guide to Their History, Chemistry, Use, and Abuse* (New York: Penguin Group, 2001), 36.

21. United States Patent Office, patent no. 2,130,523, September 20, 1938, https://patentimages.storage.googleapis.com/19/04/3e/5792825895c30e/US2130523.pdf.

22. T. Turner, "Odds and Ends of Life in Los Angeles," *Los Angeles Times*, August 11, 1935, F30.

23. Taxation of Marijuana, House of Representatives Committee on Ways and Means, Washington, DC, May 4, 1937.

24. Taxation of Marijuana, House of Representatives Committee on Ways and Means, Washington, DC, May 4, 1937.

25. New York Mayor's Committee on Marihuana and the New York Academy of Medicine, "The Marihuana Problem in the City of New York," 1944.

26. New York Mayor's Committee on Marihuana and the New York Academy of Medicine, "Marihuana Problem."

27. Single Convention on Narcotic Drugs, New York, March 30, 1961.

28. R. Nixon, "Remarks on Signing the Comprehensive Drug Abuse and Control Act of 1970," *American Presidency Project*, October 27, 1970, http://www.presidency.ucsb.edu/ws/?pid=2767.

29. Controlled Substances Act, 2 U.S.C., Section 801 (a), 811, 812; Department of Justice, Drug Enforcement Administration, "Schedules of Controlled Substances: Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [D-9-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules from Schedule II to Schedule III," *Federal Register* 64, no. 127 (July 2, 1999): 35928–30.

30. United States Commission on Marihuana and Drug Abuse, *Marihuana: A Signal of Misunderstanding* (Washington, DC: US Government Printing Office, 1972).

31. D. Baum, "Legalize It All: How to Win the War on Drugs," *Harper's Bazaar* (April 2016).

32. J. M. Cole, "Memorandum for All United States Attorneys: Guidance Regarding Marijuana Enforcement," April 29, 2013, https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf.

33. Office of the Secretary, US Department of Agriculture; Drug Enforcement Administration, Department of Justice; and Food and Drug Administration, Health and Human Services, "Statement of Principles on Industrial Hemp: A Notice by the Agriculture Department, the Drug Enforcement Administration, and the Food and Drug Administration," *Federal Register* (August 12, 2016), https://nifa.usda.gov/industrial-hemp.

34. H. Amdt. 748 to H.R. 4660, 113th Cong. (2013–2014), https://www.congress.gov/amendment/113th-congress/house-amendment/748.

35. J. B. Sessions, "Memorandum for All United States Attorneys: Marijuana Enforcement," January 4, 2018, https://www.justice.gov/opa/press-release/file/1022196/download.

36. CARERS Act of 2017, S. 1764, 115th Cong. (2017), https://www.congress.gov/bill/115th-

congress/senate-bill/1764/cosponsors?overview=closed#tabs.

37. Cory Booker: United States Senator for New Jersey, “Lawmakers Reintroduce Bipartisan, Bicameral Medical Marijuana Bill,” June 15, 2017, https://www.booker.senate.gov/?p=press_release&id=613.

38. Sessions, “Memorandum.”

39. M. A. Bachhuber, B. Saloner, C. O. Cunningham, and C. L. Barry, “Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010,” *Journal of the American Medical Association: Internal Medicine* 174, no. 10 (2014): 1668–73.

40. E. Gavrilova, T. Kamada, and F. Zoutman, “Is Legal Pot Crippling Mexican Drug Trafficking Organisations? The Effect of Medical Marijuana Laws on US Crime,” *Economic Journal* (November 16, 2017), http://onlinelibrary.wiley.com/doi/10.1111/ecoj.12521/full; J. Doward, “Legal Marijuana Cuts Violence, Says US Study, as Medical-Use Laws See Crime Fall,” *Guardian*, January 13, 2018.

41. Centers for Disease Control and Prevention, “New Research Reveals the Trends and Risk Factors behind America’s Growing Heroin Epidemic,” July 7, 2015, https://www.cdc.gov/media/releases/2015/p0707-heroin-epidemic.html.

CHAPTER 2

1. B. Rogers, “Justin Trudeau Confirms That Canada’s Marijuana Legalization Date Won’t Actually Be July 1st, 2018,” *Narcity*, 2018, https://www.narcity.com/news/justin-trudeau-confirms-that-canadas-marijuana-legalization-date-wont-actually-be-july-1st-2018; G. Ramsey, “Getting Regulation Right: Assessing Uruguay’s Historic Cannabis Initiative,” *Washington Office on Latin America*, November 2016. http://druglawreform.info/en/issues/cannabis/item/7254-getting-regulation-right.

2. Diario Oficial de la Federación, “Decreto Por el Que se Reforman y Adicionan Diversas Disposiciones de la Ley General de Salud y del Código Penal Federal,” June 19, 2017, http://www.dof.gob.mx/nota_detalle.php?codigo=5487335&fecha=19/06/2017; S. Elliott, “Mexico Just Legalized Medical Marijuana: But There’s a Catch,” *Herb*, June 19, 2017, https://herb.co/marijuana/news/mexico-legalized-medical-marijuana.

3. R. Barreiro, “Argentina Gives Green Light to Use of Medical Marijuana,” *El País*, March 30, 2017, https://elpais.com/elpais/2017/03/30/inenglish/1490870431_851473.html; Australian Associated Press, “Australia Aims to Be World’s Top Medicinal Cannabis Supplier after Exports Get Green Light,” *Guardian*, January 3, 2018, https://www.theguardian.com/society/2018/jan/04/australia-aims-to-be-worlds-top-medicinal-cannabis-supplier-after-exports-get-green-light; C. Attanasio, “Chile Marijuana Legalization: Michelle Bachelet Removes Weed from ‘Hard Drug’ List, Approves Medical Pot,” *Latin Times*, December 7, 2015, http://www.latintimes.com/chile-marijuana-legalization-michelle-bachelet-removes-weed-hard-drug-list-approves-357337; Reuters Staff, “Chilean Pharmacies Begin Marijuana Medicine Sales in First for Latam,” *Reuters*, May 10, 2017, https://www.reuters.com/article/us-chile-marijuana/chilean-pharmacies-begin-marijuana-medicine-sales-in-first-for-latam-idUSKBN1862OE; Associated Press, “Colombian President Signs Decree to Legalise Medical Marijuana,” *Guardian*, December 22, 2015, https://www.theguardian.com/world/2015/dec/22/colombia-president-legalise-medical-marijuana; S. Milekic, “Croatia Legalises Marijuana for Medical Use,” *Balkan Insight*, October 15, 2015, http://www.balkaninsight.com/en/article/croatia-first-balkan-county-to-legalize-medical-marijuana-10-15-2015-1; N. Lindsey, “Croatia’s Groundbreaking Medical Cannabis Laws Make Global Impact,” *Green Rush Daily*, June 24, 2016, https://greenrushdaily.com/croatia-makes-medical-marijuana-history; Marijuana Doctors,

"Medical Marijuana in Finland," 2018, https://www.marijuanadoctors.com/international-patients/finland; D. London, "Germany Legalizes Cannabis Prescriptions," *Marijuana.com*, January 19, 2017, https://www.marijuana.com/news/2017/01/germany-legalizes-cannabis-prescriptions; J. Hiltz, "Greece Legalizes Medical Marijuana," *Marijuana.com*, July 5, 2017, https://www.marijuana.com/news/2017/07/greece-legalizes-medical-marijuana; M. Arnold, "Greece Moves Forward on Legalizing Medical Use," *Cannabis Industry Journal*, January 23, 2018, https://www.cannabisindustryjournal.com/news_article/greece-moves-forward-on-legalizing-medical-use; Marijuana Doctors, "Updates to Medical Marijuana Program in Israel," October 4, 2017, https://www.marijuanadoctors.com/blog/israel-medical-marijuana-program-updates; J. Hiltz, "1,600 New Reasons to Celebrate Medical Marijuana in Italy," *Marijuana.com*, September 26, 2016, https://www.marijuana.com/news/2016/09/1600-new-reasons-to-celebrate-medical-marijuana-in-italy; Ministry of Justice, Government of Jamaica, "Fact Sheet Prepared by the Ministry of Justice on the Dangerous Drugs (Amendment) Act of 2015," http://moj.gov.jm/news/dangerous-drugs-amendment-act-2015-fact-sheet; S. Berg, "Norway," *International Association for Cannabinoid Medicines*, July 28, 2014, https://www.cannabis-med.org/index.php?tpl=page&id=289&lng=en; Reuters Staff, "Peru Congress Passes Bill to Legalize Medical Marijuana," *Reuters*, October 20, 2017, https://www.reuters.com/article/us-peru-marijuana/peru-congress-passes-bill-to-legalize-medical-marijuana-idUSKBN1CP1JP; J. Hiltz, "Poland Legalizes Medical Marijuana," *Marijuana.com*, July 21, 2017. https://www.marijuana.com/news/2017/07/poland-legalizes-medical-marijuana; MedicalMarijuana.eu, "Guide to Cannabis for Chronic Pain Patients in Europe," 2016, http://irka.org.rs/wp-content/uploads/2014/09/Guide-to-Cannabis-for-Chronic-Pain-Patients-in-Europe.pdf; Redazione, "San Marino Legalizza la Cannabis Terapeutica (e intende anche produrla)," *Dolce Vita Online*, June 29, 2016, http://www.dolcevitaonline.it/san-marino-ha-legalizzato-la-cannabis-terapeutica-e-intende-anche-produrla; M. Raschi, "Marijuana Coltivata a San Marino per Curare I Malati," *Il Resto del Carlino*, July 18, 2016, http://www.ilrestodelcarlino.it/rimini/cronaca/cannabis-marijuana-san-marino-1.2357222; Smokers Club, "Turkey Legalized a Farm of Medical Marijuana," March 1, 2016, http://www.thesmokersclub.com/news/international-news/turkey-legalized-a-form-of-medical-marijuana; "Cultivation of Cannabis for Medicinal Purposes is Legal in Zambia—Home Affairs Minister," *Lusaka Times*, March 2, 2017, https://www.lusakatimes.com/2017/03/02/cultivation-cannabis-medicinal-purposes-legal-zambia-home-affairs-minister.

4. L. Priya S, "5 Most Interesting Private Member Bills of 2017," *Better India*, January 4, 2018, https://www.thebetterindia.com/126700/5-private-member-bills-2017-passed-parliament.

5. European Monitoring Centre for Drugs and Drug Addiction, "Austria: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/austria/drug-laws-and-offences_en; MedicalMarijuana.eu, "Guide to Cannabis"; European Monitoring Centre for Drugs and Drug Addiction, "Belgium: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/belgium/drug-laws-and-offences_en; MedicalMarijuana.eu, "Guide to Cannabis"; TNI Drugs and Democracy Programme, "Belize GG Assents to Legislation Allowing for Decriminalisation of Marijuana," November 4, 2017, http://druglawreform.info/en/country-information/caribbean/belize; TNI Drugs and Democracy Programme, "Brazil," http://druglawreform.info/en/country-information/latin-america/brazil/item/201-brazil; Associated Press, "Colombian President Signs Decree"; TNI Drugs and Democracy Programme, "Costa Rica," http://druglawreform.info/en/country-information/central-america/costa-rica; European Monitoring Centre for Drugs and Drug Addiction, "Czech Republic: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/czech-republic/drug-laws-and-offences_en; MedicalMarijuana.eu, "Guide to Cannabis"; TNI Drugs and Democracy Programme, "Ecuador," http://druglawreform.info/en/country-information/latin-america/ecuador; E. Pachico, "Why Did Ecuador Toughen Up Drug Laws?" *InSight Crime*, October 3, 2015,

https://www.insightcrime.org/news/brief/why-did-ecuador-toughen-up-drug-laws; Agenda.ge, "Court Abolishes Imprisonment for Sowing of Cannabis for Personal Use," July 14, 2017, https://agenda.ge/news/83501/eng; Ministry of Justice, Government of Jamaica, "Fact Sheet"; European Monitoring Centre for Drugs and Drug Addiction, "Latvia: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/latvia/drug-laws-and-offences_en; European Monitoring Centre for Drugs and Drug Addiction, "Lithuania: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/lithuania/drug-laws-and-offences_en; D. London, "Luxembourg Prime Minister Promises Medical Marijuana," *Marijuana.com*, October 30, 2017, https://www.marijuana.com/news/2017/10/luxembourg-prime-minister-promises-medical-marijuana; European Monitoring Centre for Drugs and Drug Addiction, "Luxembourg: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/luxembourg/drug-laws-and-offences_en; European Monitoring Centre for Drugs and Drug Addiction, "Malta: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/malta/drug-laws-and-offences_en; MedicalMarijuana.eu, "Guide to Cannabis"; TNI Drugs and Democracy Programme, "Mexico," http://druglawreform.info/en/country-information/mexico/item/205-mexico; European Monitoring Centre for Drugs and Drug Addiction, "Moldova Country Overview," http://www.emcdda.europa.eu/countries/moldova_en#laws; MedicalMarijuana.eu, "Guide to Cannabis"; TNI Drugs and Democracy Programme, "Paraguay: Decriminalization," http://druglawreform.info/en/country-information/latin-america/paraguay/item/206-paraguay; European Monitoring Centre for Drugs and Drug Addiction, "Portugal: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/portugal/drug-laws-and-offences_en; C. Ingraham, "Portugal Decriminalised Drugs 14 Years Ago—and Now Hardly Anyone Dies from Overdosing," *Independent*, June 6, 2015, http://www.independent.co.uk/news/world/europe/portugal-decriminalised-drugs-14-years-ago-and-now-hardly-anyone-dies-from-overdosing-10301780.html; MedicalMarijuana.eu, "Guide to Cannabis"; European Monitoring Centre for Drugs and Drug Addiction, "Slovenia Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/slovenia/drug-laws-and-offences_en; MedicalMarijuana.eu, "Guide to Cannabis"; European Monitoring Centre for Drugs and Drug Addiction, "Spain Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/spain/drug-laws-and-offences_en; MedicalMarijuana.eu, "Guide to Cannabis"; MedicalMarijuana.eu, "Guide to Cannabis"; MedicalMarijuana.eu, "Guide to Cannabis"; TNI Drugs and Democracy Programme, "Venezuela," http://druglawreform.info/en/country-information/latin-america/venezuela.

6. "France to Issue On-the-Spot Fines for Cannabis Use," *France 24*, January 25, 2018, http://www.france24.com/en/20180125-france-cannabis-drugs-spot-fines-collomb-macron.

7. European Monitoring Centre for Drugs and Drug Addiction, "Greece: Country Drug Report 2017," http://www.emcdda.europa.eu/countries/drug-reports/2017/greece_en.

8. World Health Organization, "WHO Recommends the Most Stringent Level of International Control for Synthetic Opioid Carfentanil," December 13, 2017, http://www.who.int/medicines/news/2017/WHO-recommends-most-stringent-level-int-control/en.

9. *Conant v. Walters*, 309 F.3d 629 (9th Cir. 2002).

10. State of Connecticut, House Bill No. 5389, Public Act No. 12-55, 2012, https://www.cga.ct.gov/2012/ACT/PA/2012PA-00055-R00HB-05389-PA.htm.

11. Public Law 33-220 343-33 (COR), http://www.guamlegislature.com/Public_Laws_33rd/P.L.%20No.%2033-220.pdf.

12. J. Sabian, "Medical Marijuana Rules and Regulations Signed into Law," *Pacific Daily News*, February 14, 2018, https://www.guampdn.com/story/news/2018/02/14/medical-marijuana-rules-and-regulations-signed-into-law/335916002.

13. Illinois Department of Public Health, “Medical Cannabis Patient Registry Program,” http://www.dph.illinois.gov/topics-services/prevention-wellness/medical-cannabis.

14. Illinois Department of Public Health, “Debilitating Conditions,” November 1, 2016, http://www.dph.illinois.gov/topics-services/prevention-wellness/medical-cannabis/debilitating-conditions.

15. Minnesota Department of Health, Office of Medical Cannabis, “Medical Cannabis and Intractable Pain,” December 2, 2015, http://www.health.state.mn.us/topics/cannabis/intractable/intractablepainfs.pdf.

16. New Jersey Compassionate Use Medical Marijuana Act, 2010, ftp://www.njleg.state.nj.us/20082009/S0500/119_R3.htm.

17. BDO, “Newsletter: Medical Cannabis in Puerto Rico and Taxation,” August 11, 2017, http://www.bdopr.com/en-gb/insights/tax/tax-alert/medical-cannabis-in-puerto-rico-and-taxation.

18. Alabama State Legislature, House Bill 61, 2016, https://legiscan.com/AL/text/HB61/2016.

19. Georgia General Assembly, SB 16, 2017–2018, http://www.legis.ga.gov/Legislation/en-US/display/20172018/SB/16.

20. Indiana General Assembly, House Bill 1148, 2017, https://iga.in.gov/legislative/2017/bills/house/1148#document-f1053500.

21. Iowa Legislature, House File 524, 2017, https://www.legis.iowa.gov/legislation/BillBook?ga=87&ba=hf524.

22. Americans for Safe Access, “Kentucky Legal Information,” http://www.safeaccessnow.org/kentucky_legal_information.

23. Louisiana State Legislature, Senate Bill No. 271, 2016, http://www.legis.la.gov/legis/ViewDocument.aspx?d=1003807.

24. Mississippi Code §41-29-139, 2014, https://law.justia.com/codes/mississippi/2014/title-41/chapter-29/article-3/section-41-29-139.

25. Mississippi Legislature, House Bill 1231, 2014, http://billstatus.ls.state.ms.us/documents/2014/html/HB/1200-1299/HB1231SG.htm.

26. North Carolina General Assembly, House Bill 1220/SL 2014-53, 2013–2014, https://www.ncleg.net/gascripts/BillLookUp/BillLookUp.pl?Session=2013&BillID=HB1220.

27. North Carolina General Assembly, House Bill 766/SL 2015-154, 2015–2016, https://www.ncleg.net/gascripts/BillLookUp/BillLookUp.pl?Session=2015&BillID=HB+766.

28. State of Oklahoma, House Bill No. 2835, 2016, http://webserver1.lsb.state.ok.us/cf_pdf/2015-16%20ENR/hB/HB2835%20ENR.PDF.

29. South Carolina General Assembly, A221, R229, S1035, 2014, http://www.scstatehouse.gov/sess120_2013-2014/bills/1035.htm.

30. J. Holland, “Daugaard: Yes on Teacher Pay, Yes on Medicaid Expansion, No on Medical Marijuana,” *Rapid City Journal*, January 11, 2016, http://rapidcityjournal.com/news/local/gov-daugaard-yes-on-teacher-pay-yes-on-medicaid-expansion/article_640effab-2379-58b5-b078-124c4d5c6fe9.html.

31. J. Ebert, “Republicans Introduce Bill to Allow Medical Marijuana in Tennessee,” *Tennessean*, January 18, 2018, https://www.tennessean.com/story/news/politics/2018/01/18/republicans-introduce-bill-expand-medical-marijuana-tennessee/1044287001.

32. M. Bud, “Texas to Roll Out First CBD Sales by End of Year,” *Marijuana.com*, November 27, 2017, https://www.marijuana.com/news/2017/11/texas-to-roll-out-first-cbd-sales-by-end-of-year.

33. Texas Department of Public Safety, “Compassionate Use Program,” https://www.dps.texas.gov/rsd/CUP/index.htm.

34. Utah State Legislature, H.B. 105, 2014, https://le.utah.gov/~2014/bills/static/hb0105.html.

35. Virginia General Assembly, H.B. 1445, 2015, https://lis.virginia.gov/cgi-bin/legp604.exe?151+sum+HB1445.

36. Wisconsin State Legislature, Assembly Bill 726, 2013–2014, https://docs.legis.wisconsin.gov/2013/proposals/ab726.

37. Wyoming State Legislature, Bill No. HB0032, 2015, http://legisweb.state.wy.us/2015/Enroll/HB0032.pdf

38. E. Guo, "Staunchly Anti-Pot Idaho Introduces Legislation to Allow CBD Oil," *Inverse Culture*, January 26, 2018, https://www.inverse.com/article/40578-idaho-legislation-cbd-oil

39. M. Riedl, "City Gives Initial OK on Marijuana Ordinance" *Wichita Eagle*, June 6, 2017, http://www.kansas.com/news/politics-government/article154613664.html.

40. Veterans Equal Access Act, H.R. 1820, 115th Cong. (2017), https://www.congress.gov/bill/115th-congress/house-bill/1820.

41. Industrial Hemp Farming Act of 2017, H.R. 3530, 115th Cong. (2017).

42. CARERS Act of 2017, S. 1764, 115th Cong. (2017).

43. Marijuana Justice Act of 2017, S. 1689, 115th Cong. (2017).

44. Therapeutic Hemp Medical Access Act of 2017, S. 1008, 115th Cong." www.GovTrack.us. (2017).

45. Medical Marijuana Research Act of 2017, H.R. 3391, 115th Cong. (2017).

CHAPTER 3

1. J. M. McPartland, I. Matias, V. Di Marzo, and M. Glass, "Evolutionary Origins of the Endocannabinoid System," *Gene* 370 (2006): 64–74, doi:10.1016/j.gene.2005.11.004.

2. E. B. Russo, "Clinical Endocannabinoid Deficiency (CECD): Can This Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and Other Treatment-Resistant Conditions?" *Neuroendocrinology Letters* 25, nos. 1–2 (2003): 31–39.

3. P. Pacher, S. Bátkai, and G. Kunos. "The Endocannabinoid System as an Emerging Target of Pharmacotherapy," *Pharmacological Reviews* 58, no. 3 (2006): 389–462.

4. J. McPartland, "The Endocannabinoid System: An Osteopathic Perspective," *Journal of the American Osteopathic Association* 108, no. 10 (October 2008): 586–600, doi:10.7556/jaoa.2008.108.10.586.

5. F. Rodríguez de Fonseca, I. Del Arco, F. J. Bermudez-Silva, A. Bilbao, A. Cippitelli, and M. Navarro, "The Endocannabinoid System: Physiology and Pharmacology," *Alcohol and Alcoholism* 40, no. 1 (2005): 2–14.

6. M. A. ElSohly and D. Slade, "Chemical Constituents of Marijuana: The Complex Mixture of Natural Cannabinoids," *Life Sciences* 78, no. 5 (2005) 539–548.

7. E. Ryberg, N. Larsson, S. Sjögren, et al., "The Orphan Receptor GPR55 Is a Novel Cannabinoid Receptor," *British Journal of Pharmacology* 152, no. 7 (2007): 1092–1101.

8. L. De Petrocellis, A. Ligresti, A. S. Moriello, et al., "Effects of Cannabinoids and Cannabinoid-Enriched *Cannabis* Extracts on TRP Channels and Endocannabinoid Metabolic Enzymes," *British Journal of Pharmacology* 163, no. 7 (2011): 1479–94.

9. V. Di Marzo, D. Melck, T. Bisogno, and L. De Petrocellis, "Endocannabinoids: Endogenous Cannabinoid Receptor Ligands with Neuromodulatory Action," *Trends in Neurosciences* 21, no. 12 (December 1998): 521–28.

10. A. Calignano, G. La Rana, A. Giuffrida, and D. Piomelli, "Control of Pain Initiation by Endogenous Cannabinoids," *Nature* 394 (1998): 277–81; R. G. Pertwee, "Cannabinoid Receptors

and Pain," *Progress in Neurobiology* 63 (2001): 569–611.

11. D. Piomelli, "The Molecular Logic of Endocannabinoid Signaling," *Nature Reviews Neuroscience* 4 (2003): 873–84.

12. V. Di Marzo, et al., "Endocannabinoids"; F. Rodríguez de Fonseca, M. Navarro, R. Gómez, et al., "An Anorexic Lipid Mediator Regulated by Feeding," *Nature* 414, no. 6860 (2001): 209–12; F. Rodríguez de Fonseca, I. Del Arco, J. L. Martin-Calderon, M. A. Gorriti, and M. Navarro, "Role of the Endogenous Cannabinoid System in the Regulation of Motor Activity," *Neurobiology of Disease* 5 (1998): 483–501; F. Chaperon and M.-H. Thiébot, "Behavioral Effects of Cannabinoid Agents in Animals," *Critical Reviews in Neurobiology* 13 (1999): 243–81; C. Castellano, C. Rossi-Arnaud, V. Cestari, and M. Costanzi, "Cannabinoids and Memory: Animal Studies," *Current Drug Targets—CNS and Neurological Disorders* 2 (2003): 389–402; A. A. Izzo, N. Mascolo, and F. Capasso, "The Gastrointestinal Pharmacology of Cannabinoids," *Current Opinion in Pharmacology* 1, no. 6 (December 2001): 597–603, https://doi.org/10.1016/S1471-4892(01)00102-3; G. A. Cabral, "Marijuana and Cannabinoids: Effects on Infections, Immunity and AIDS," *Journal of Cannabis Therapeutics* 1 (2001): 61–85.

13. W. A. Devane, L. Hanus, A. Breuer, et al., "Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor," *Science* 258 (1992): 1946–49.

14. V. Di Marzo, A. Fontana, H. Cadas, et al., "Formation and Inactivation of Endogenous Cannabinoid Anandamide in Central Neurons," *Nature* 372 (1994): 686–91.

15. A. Berger, G. Crozier, and T. Bisogno, "Anandamide and Diet: Inclusion of Dietary Arachidonate and Docosahexaenoate Leads to Increased Brain Levels of the Corresponding *N*-Acylethanolamines in Piglets," *National Academy of Sciences* 98, no. 11 (May 2001): 6402–6.

16. R. Mechoulam and S. Ben-Shabat, "From Gan-Zi-Gun-Nu to Anandamide and 2-Arachidonoylglycerol: The Ongoing Story of Cannabis," *Natural Product Reports* 16 (1999): 131–43.

17. N. Stella, P. Schweitzer, and D. Piomelli, "A Second Endogenous Cannabinoid That Modulates Long-Term Potentiation," *Nature* 388 (1997): 773–78.

18. T. Sugiura, S. Kondo, A. Sukagawa, et al., "2-Arachidonoylglycerol: A Possible Endogenous Cannabinoid Receptor Ligand in Brain," *Biochemistry Biophysics Research Communications* 215 (1995): 89–97.

19. T. P. Dinh, D. Carpenter, F. M. Leslie, et al., "Brain Monoglyceride Lipase Participating in Endocannabinoid Inactivation," *Proceedings of the National Academy of Sciences of the United States of America* 99 (2002): 10819–24.

20. R. Upton, L. Craker, M. ElSohly, A. Romm, E. Russo, and M. Sexton, eds., *Cannabis Inflorescence (*Cannabis *spp.): Standards of Identity, Analysis, and Quality Control*, rev. (Scotts Valley, CA: American Herbal Pharmacopoeia, 2014).

21. R. Brenneisen, "Cannabis and Analysis of Phytocannabinoids and Other Cannabis Constituents," in *Marijuana and the Cannabinoids*, ed. M. A. ElSohly (Totowa, NJ: Humana Press, 1984), 40.

22. S. Ben-Shabat, E. Fride, T. Sheskin, et al., "An Entourage Effect: Inactive Endogenous Fatty Acid Glycerol Esters Enhance 2-Arachidonoyl-Glycerol Cannabinoid Activity," *European Journal of Pharmacology* 353, no. 1 (1998): 23–31.

23. R. C. Clarke and D. P. Watson, "Cannabis and Natural Cannabis Medicines," in *Marijuana and the Cannabinoids*, ed. M. A. ElSohly (Totowa, NJ: Humana Press, 1984), 5–6.

24. D. Meiri, "Matching an Effective Cannabis Strain Extract for a Specific Subtype of Cancer," CannMed Presentation, 2017.

25. S. Takeda, "Cannabidiolic Acid-Mediated Selective Down-Regulation of C-Fos in Highly Aggressive Breast Cancer MDA-MB-231 Cells: Possible Involvement of Its Down-Regulation in the Abrogation of Aggressiveness," *Journal of Natural Medicine* 71 no. 1 (January 2017): 286–

91, doi: 10.1007/s11418-016-1030-0.

26. S. Takeda, K. Misawa, I. Yamamoto, and K. Watanabe, “Cannabidiolic Acid as a Selective Cyclooxygenase-2 Inhibitory Component in Cannabis,” *Drug Metabolism and Disposition* 36 no. 9 (2008): 1917–21, http://doi.org/10.1124/dmd.108.020909.

27. E. M. Rock and L. A. Parker, “Synergy between Cannabidiol, Cannabidiolic Acid, and Δ9-Tetrahydrocannabinol in the Regulation of Emesis in the *Suncus murinus* (House Musk Shrew),” *Behavioral Neuroscience* 129, no. 3 (2015): 368–70.

28. I. G. Karniol, I. Shirakawa, and R. N. Takahashi, “Effects of Delta-9-Tetrahydrocannabinol and Cannabinol in Man,” *Pharmacology* 13, no. 6 (1975): 502–12.

29. L. L. Iversen, *The Science of Marijuana* (New York: Oxford University Press, 2008), 56–65.

30. R. G. Pertwee, “The Diverse CB1 and CB2 Receptor Pharmacology of Three Plant Cannabinoids: D9-Tetrahydrocannabinol, Cannabidiol and D9-Tetrahydrocannabivarin,” *British Journal of Phamacology* 153, no. 2 (2008): 199–215.

31. O. Devinsky et al., “Cannabidiol: Pharmacology and Potential Therapeutic Role in Epilepsy and Other Neuropsychiatric Disorders,” *Epilepsia* 55, no. 6 (2014): 791–802.

32. I. G. Karniol and E. A. Carlini, “Pharmacological Interaction between Cannabidiol and δ9-Tetrahydrocannabinol,” *Psychopharmacologia* 33, no. 1 (1973): 53–70, https://doi.org/10.1007/BF00428793.

33. N. Shinjyo and V. Di Marzo, “The Effect of Cannabichromene on Adult Neural Stem/Progenitor Cells,” *Neurochemistry International* 63, no. 5 (2013): 432–37, doi:10.1016/j.neuint.2013.08.002.

34. E. Russo, “Taming THC: Potential Cannabis Synergy and Phytocannabinoid-Terpenoid Entourage Effects,” *British Journal of Pharmacology* 163, no. 7 (August 2011): 1344–64, doi: 10.1111/j.1476-5381.2011.01238.x.

35. J. K. Booth, J. E. Page, and J. Bohlmann, “Terpene Synthases from *Cannabis sativa*,” *PLoS One* 12, no. 3 (2017): e0173911, doi: 10.1371/journal.pone.0173911; C. M. Andre, “*Cannabis sativa*: ‘The Plant of the Thousand and One Molecules,’” *Frontiers in Plant Science* 7 (2016): 19, doi:10.3389/fpls.2016.00019.

36. Russo, “Taming THC.”

37. S. A. Ross and M. A. ElSohly, “The Volatile Oil Composition of Fresh and Air-Dried Buds of *Cannabis sativa*,” *Journal of Natural Products* 59, no. 1 (1996): 49–51.

38. PubChem, “Caryophyllene,” https://pubchem.ncbi.nlm.nih.gov/compound/5281515#section=Literature.

39. B. Horváth, P. Mukhopadhyay, M. Kechrid, et al., “β-Caryophyllene Ameliorates Cisplatin-Induced Nephrotoxicity in a Cannabinoid 2 Receptor-Dependent Manner,” *Free Radical Biology and Medicine* 52, no. 8 (2012):1325–33, doi:10.1016/j.freeradbiomed.2012.01.014.

40. J. Gertsch, M. Leonti, S. Raduner, et al., “Beta-Caryophyllene Is a Dietary Cannabinoid,” *Proceedings of the National Academy of Sciences of the United States of America* 105, no. 26 (July 1, 2008): 9099–9104, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2449371.

41. T. Komori, R. Fujiwara, M. Tanida, et al., “Effects of Citrus Fragrance on Immune Function and Depressive States,” *Neuroimmunomodulation* 2 (1995): 174–80.

42. PubChem, “D-Limonene,” https://pubchem.ncbi.nlm.nih.gov/compound/440917.

43. P. L. Crowell, C. E. Elson, H. H. Bailey, A. Elegbede, J. D. Haag, and M. N. Gould, “Human Metabolism of the Experimental Cancer Therapeutic Agent D-Limonene,” *Cancer Chemotherapy Pharmacology* 35, no. 1 (1994): 31–37, https://www.ncbi.nlm.nih.gov/pubmed/7987974.

44. H. Igimi, T. Hisatsugu, and M. Nishimura, “The Use of *D*-Limonene Preparation as a

Dissolving Agent of Gallstones," *American Journal of Digestive Diseases* 21, no. 11 (November 1976): 926–39, https://doi.org/10.1007/BF01071903.

45. J. V. A. Santiago, J. Jayachitra, M. Shenbagam, and N. Nalini, "Dietary D-Limonene Alleviates Insulin Resistance and Oxidative Stress-Induced Liver Injury in High-Fat Diet and L-NAME-Treated Rats," *European Journal of Nutrition* 51, no. 1 (February 2012): 57–68, doi: 10.1007/s00394-011-0182-7.

46. A. C. Rivas del Silva, P. M. Lopes, M. M. Barros de Azevedo, D. C. Costa, C. S. Alviano, and D. S. Alviano, "Biological Activities of α-Pinene and β-Pinene Enantiomers," *Molecules* 17, no. 6 (May 25, 2012): 6305–16, doi: 10.3390/molecules17066305.

47. Brenneisen, "Chemistry and Analysis," 40.

48. PubChem, "Beta-Ocimene," https://pubchem.ncbi.nlm.nih.gov/compound/_E_-beta-ocimene#section=Pharmacology-and-Biochemistry.

49. J. Dach, E. A. Moore, and J. Kander, *Cannabis Extracts in Medicine* (Jefferson, NC: McFarland, 2015), 79.

50. P. Taupin, "Apigenin and Related Compounds Stimulate Adult Neurogenesis: Mars, Inc., the Salk Institute for Biological Studies," *Expert Opinion on Therapeutic Patents* 19 (2009): 523–27.

51. Y. Lin, R. Shi, X. Wang, and H. M. Shen, "Luteolin, a Flavonoid with Potential for Cancer Prevention and Therapy," *Current Cancer Drug Targets* 8, no. 7 (November 2008): 634–46.

52. L. Törmäkangas, P. Vuorela, E. Saario, M. Leinonen, P. Saikku, and H. Vuorela, "In Vivo Treatment of Acute Chlamydia pneumoniae Infection with the Flavonoids Quercetin and Luteolin and an Alkyl Gallate, Octyl Gallate, in a Mouse Model," *Biochemical Pharmacology* 70 (November 2005): 1222–30, doi:10.1016/j.bcp.2005.07.012.

53. H. Kirmizibekmez, I. Atay, M. Kaiser, et al., "Antiprotozoal Activity of Melampyrum arvense and its Metabolites," *Phytotherapy Research* 25, no. 1 (July 7, 2010): 142–46, doi:10.1002/ptr.3233.

54. U. Nöthlings, S. P. Murphy, L. R. Wilkens, B. E. Henderson, and L. N. Kolonel, "Flavonols and Pancreatic Cancer Risk: The Multiethnic Cohort Study," *American Journal of Epidemiology* 166, no. 8, (October 15, 2007): 924–31, https://doi.org/10.1093/aje/kwm172.

55. B. M. Ford, S. Tai, W. E. Fantegrossi, and P. L. Prather, "Synthetic Pot: Not Your Grandfather's Marijuana," *Trends in Pharmacological Sciences* 38, no. 3 (March 2017): 257–76.

CHAPTER 4

1. G. R. Thompson, J. M. Tuscano, M. Dennis, et al., "A Microbiome Assessment of Medical Marijuana," *Clinical Microbiology and Infection* 23, no. 4 (April 2017): 269–70, http://dx.doi.org/10.1016/j.cmi.2016.12.001.

2. California Comprehensive Medical Cannabis Regulation and Safety Act 2016.

3. D. L. Palliyaguru and F. Wu, "The Global Geographical Overlap of Aflatoxin and Hepatitis C: Controlling Risk Factors for Liver Cancer Worldwide," *Food Additives and Contaminants, Part A: Chemistry, Analysis, Control, Exposure and Risk Assessment* 30, no. 3 (2013): 534–40.

4. A. Kavalier, chief scientific officer, Holistic Industries, e-mail message to author, January 25, 2018.

5. Personal conversation with Adam Kavalier

6. A. Lozano, "Pesticides in Marijuana Growing Pose a Growing Problem for Cannabis Consumers," *Los Angeles Weekly*, October 27, 2016.

7. Colorado Statewide Marijuana Pesticides Policy Statement, November 12, 2015, https://www.colorado.gov/pacific/sites/default/files/atoms/files/Statewide%20Marijuana%20Pesti

CHAPTER 5

1. American Academy of Pain Medicine, "AAPM Facts and Figures on Pain," http://www.painmed.org/PatientCenter/Facts_on_Pain.aspx.

2. C. Reinarman, H. Nunberg, F. Lanthier, and T. Heddleston, "Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics," *Journal of Psychoactive Drugs* 43, no. 2 (2011): 128–35.

3. National Center for Injury Prevention and Control, "Annual Surveillance Report of Drug-Related Risks and Outcomes," 2017.

4. H. Hedegaard, M. Warner, and A. M. Miniño, "Drug Overdose Deaths in the United States, 1999–2016," NCHS Data Brief, no. 294, December 2017, https://www.cdc.gov/nchs/products/databriefs/db294.htm.

5. M. A. Bachhuber, B. Saloner, C. O. Cunningham, and C. L. Barry, "Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010," *JAMA Internal Medicine* 174, no. 10 (October 2014): 1668–73, doi:10.1001/jamainternmed.2014.4005.

6. Office of Governor Larry Hogan, "Hogan-Rutherford Administration Declares State of Emergency, Announces Major Funding to Combat Heroin and Opioid Crisis in Maryland," Press Release, March 1, 2017, http://governor.maryland.gov/2017/03/01/hogan-rutherford-administration-declares-state-of-emergency-announces-major-funding-to-combat-heroin-and-opioid-crisis-in-maryland.

7. A. E. Dubin and A. Patapoutian, "Nociceptors: The Sensors of the Pain Pathway," *Journal of Clinical Investigation* 120, no. 11 (2010): 3760–72.

8. K. P. Hill, M. D. Palastro, B. Johnson, and J. W. Ditre, "Cannabis and Pain: A Clinical Review," *Cannabis and Cannabinoid Research* 2, no. 1 (May 2017): 96–104, doi:10.1089/can.2017.0017.

9. J. M. Zhang and J. An, "Cytokines, Inflammation and Pain," *International Anesthesiology Clinics* 45, no. 2 (2007): 27–37.

10. C. Rivat, C. Becker, A. Blugeot, et al., "Chronic Stress Induces Transient Spinal Neuroinflammation, Triggering Sensory Hypersensitivity and Long-Lasting Anxiety-Induced Hyperalgesia," *Journal of Pain* 150, no. 2 (August 2010): 358–68; K. Wiech and I. Tracey, "The Influence of Negative Emotions on Pain: Behavioral Effects and Neural Mechanisms," *NeuroImage* 47, no. 3 (September 2009): 987–94.

11. M. Lee, S. M. Silverman, H. Hansen, V. B. Patel, and L. Manchikanti, "A Comprehensive Review of Opioid-Induced Hyperalgesia," *Pain Physician* 14 (2011): 145–61.

12. D. I. Abrams, P. Couey, S. B. Shade, M. E. Kelly, and N. L. Benowitz, "Cannabinoid-Opioid Interaction in Chronic Pain," *Clinical Pharmacology and Therapeutics* 90, no. 6 (December 2011): 844–51, doi:10.1038/clpt.2011.188.

13. P. Lucas, "Cannabis as an Adjunct to or Substitute for Opiates in the Treatment of Chronic Pain," *Journal of Psychoactive Drugs* 44, no. 2 (April–June 2012): 125–33.

14. M. A. Ware, T. Wang, S. Shapiro, et al., "Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial," *Canadian Medical Association Journal* 182, no. 14 (2010): E694–E701.

15. F. Grotenhermen and K. Muller-Vahl, "The Therapeutic Potential of Cannabis and Cannabinoids," *Deutsches Ärzteblatt International* 109, nos. 29–30 (2012): 495–501.

16. Hill, et al., "Cannabis and Pain."

17. In randomized trials, patients are arbitrarily placed in a particular group without input from the patients or the researchers. A crossover study is when half the subjects receive the active

compound and half receive placebo. Then after those results are recorded, the subjects who received placebo get the active compound, and those who received the active compound receive placebo.

18. G. W. Booz, "Cannabidiol as an Emergent Therapeutic Strategy for Lessening the Impact of Inflammation on Oxidative Stress," *Free Radical Biology and Medicine* 51, no. 5 (2011): 1054–61.

19. E. B. Russo and G. W. Guy, "A Tale of Two Cannabinoids: The Therapeutic Rationale for Combining Tetrahydrocannabinol and Cannabidiol," *Medical Hypotheses* 66, no. 4 (2006): 234–46.

20. D. L. Christensen, J. Baio, K. Van Naarden Braun, et al., "Prevalence and Characteristics of Autism Spectrum Disorder among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012," *Morbidity and Mortality Weekly Report* 65, no. 3 (April 1, 2016): 1–23.

21. B. Chakrabarti, A. Persico, N. Battista, and M. Maccarrone, "Endocannabinoid Signaling in Autism," *Neurotherapeutics* 12, no. 4 (2015): 837–47.

22. C. T. Tart, "Marijuana Intoxication: Common Experiences," *Nature* 226 (May 23, 1970): 701–4.

23. A. M. Depino, "Peripheral and Central Inflammation in Autism Spectrum Disorders" *Molecular and Cellular Neurosciences* 53 (March 2013): 69–76, doi:10.1016/j.mcn.2012.10.003; D. L. Vargas, C. Nascimbene, and C. Krishnan, "Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism," *Annals of Neurology* 57, no. 1 (January 2005): 67–81; C. Földy, R. C. Malenka, and T. C. Südhof, "Autism-Associated Neuroligin-3 Mutations Commonly Disrupt Tonic Endocannabinoid Signaling," *Neuron* 78, no. 3 (May 2013): 498–509, doi:10.1016/j.neuron.2013.02.036.

24. K.-M. Jung, M. Sepers, C. M. Henstridge, et al., "Uncoupling of the Endocannabinoid Signalling Complex in a Mouse Model of Fragile X Syndrome," *Nature Communications* 3 (2012): 1080, doi:10.1038/ncomms2045.

25. R. Kurz and K. Blaas, "Use of Dronabinol (Delta-9-THC) in Autism: A Prospective Single-Case-Study with an Early Infantile Autistic Child," *Cannabinoids* 5, no. 4 (2010): 4–6.

26. S. Sarfaraz, V. M. Adhami, and D. N. Syed, "Cannabinoids for Cancer Treatment: Progress and Promise," *Cancer Research* 68, no 2 (January 2008): 338–42.

27. M. Guzman, "Cannabinoids: Potential Anticancer Agents," *Nature Reviews Cancer* 3, no. 10 (October 2003): 745–55, doi:10.1038/nrc1188.

28. D. A. Ladin, E. Soliman, L. Griffin, and R. Van Dross, "Preclinical and Clinical Assessment of Cannabinoids as Anti-Cancer Agents," *Frontiers in Pharmacology* 7 (2016): 361.

29. Ladin et al., "Preclinical and Clinical Assessment."

30. C. Blázquez, L. González-Feria, L. Álvarez, A. Haro, M. L. Casanova, and M. Guzmán, "Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas," *Cancer Research* 64, no. 16 (August 15, 2004): 5617–23, doi:10.1158/0008-5472.CAN-03-3927.

31. B. Romano, F. Borrelli, E. Pagano, M. G. Cascio, R. G. Pertwee, and A. A. Izzo, "Inhibition of Colon Carcinogenesis by a Standardized *Cannabis sativa* Extract with High Content of Cannabidiol," *Phytomedicine* 21, no. 5 (April 15, 2014): 631–39, doi:10.1016/j.phymed.2013.11.006.

32. A. Carracedo, M. Gironella, M. Lorente, et al., "Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress-Related Genes," *Cancer Research* 66, no. 13 (July 2006): 6748–55.

33. A. Ligresti, A. S. Moriello, K. Starowicz, et al., "Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma," *Journal of Pharmacology and Experimental Therapeutics* 318, no. 3 (September 2006): 1375–87.

34. S. Sarfaraz, F. Afaq, V. M. Adhami, A. Malik, and H. Mukhtar, “Cannabinoid Receptor Agonist-Induced Apoptosis of Human Prostate Cancer Cells LNCaP Proceeds through Sustained Activation of ERK1/2 Leading to G1 Cell Cycle Arrest,” *Journal of Biological Chemistry* 281 (2006): 39480–91.

35. B. Chakravarti, J. Ravi, and R. K. Ganju, “Cannabinoids as Therapeutic Agents in Cancer: Current Status and Future Implications,” *Oncotarget* 5, no. 15 (2014): 5852–72.

36. C. Blázquez, A. Carracedo, L. Barrado, et al., “Cannabinoid Receptors as Novel Targets for the Treatment of Melanoma,” *FASEB Journal* 20, no. 14 (December 2006): 2633–35.

37. S. T. Lukhele and L. R. Motadi, “Cannabidiol Rather than *Cannabis sativa* Extracts Inhibit Cell Growth and Induce Apoptosis in Cervical Cancer Cells,” *BMC Complementary and Alternative Medicine* 16, no. 1 (2016): 335.

38. S. Schröder, K. Beckmann, G. Franconi, et al., “Can Medical Herbs Stimulate Regeneration or Neuroprotection and Treat Neuropathic Pain in Chemotherapy-Induced Peripheral Neuropathy?” *Evidence-Based Complementary and Alternative Medicine* (2013); V. Maida and P. J. Daeninck, “A User’s Guide to Cannabinoid Therapies in Oncology,” *Current Oncology* 23, no. 6 (2016): 398–406; D. I. Abrams, “Integrating Cannabis into Clinical Cancer Care,” *Current Oncology* 23, suppl. 2 (March 2016): S8–S14.

39. A. Oláh, B. I. Tóth, I. Borbíró, et al., “Cannabidiol Exerts Sebostatic and Antiinflammatory Effects on Human Sebocytes,” *Journal of Clinical Investigation* 124, no. 9 (2014): 3713–24.

40. E. B. Russo, “Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes,” *Cannabis and Cannabinoid Research* 1, no. 1 (2016): 154–65.

41. V. Di Marzo, N. Stella, and A. Zimmer, “Endocannabinoid Signalling and the Deteriorating Brain,” *Nature Neuroscience* 16, no. 1 (January 2015): 30–42.

42. J. M. Perkins and S. N. Davis, “Endocannabinoid System Overactivity and the Metabolic Syndrome: Prospects for Treatment,” *Current Diabetes Reports* 8, no.1 (February 2008): 12–19.

43. M. A. Ruby, D. K. Nomura, C. S. Hudak, et al., “Overactive Endocannabinoid Signaling Impairs Apolipoprotein E-Mediated Clearance of Triglyceride-Rich Lipoproteins,” *Proceedings of the National Academy of Sciences* 105, no. 38 (September 2008): 14561–66, doi:10.1073/pnas.0807232105.

44. V. Di Marzo, M. Côté, I. Matias, et al., “Changes in Plasma Endocannabinoid Levels in Viscerally Obese Men Following a 1-Year Lifestyle Modification Programme and Waist Circumference Reduction: Associations with Changes in Metabolic Risk Factors,” *Diabetologia* 52, no. 2 (February 2009): 213–17, doi:10.1007/s00125-008-1178-6.

45. C. T. Costiniuk, E. Mills, and C. L. Cooper, “Evaluation of Oral Cannabinoid-Containing Medications for the Management of Interferon and Ribavirin-Induced Anorexia, Nausea and Weight Loss in Patients Treated for Chronic Hepatitis C Virus,” *Canadian Journal of Gastroenterology* 22, no. 4 (April 2008): 376–80.

46. T. F. Plasse, R. W. Gorter, S. H. Krasnow, M. Lane, K. V. Shepard, and R. G. Wadleigh, “Recent Clinical Experience with Dronabinol,” *Pharmacology Biochemistry and Behavior* 40, no. 3 (November 1991): 701–8.

47. G. Appendino, S. Gibbons, A. Giana, et al. “Antibacterial Cannabinoids from *Cannabis sativa*: A Structure-Activity Study,” *Journal of Natural Products* 71, no. 8 (August 2008): 1427–30, doi:10.1021/np8002673.

48. L. De Petrocellis, P. Orlando, A. S. Moriello, et al., “Cannabinoid Actions at TRPV Channels: Effects on TRPV3 and TRPV4 and Their Potential Relevance to Gastrointestinal Inflammation,” *Acta Physiologica* 204, no. 2 (February 2012): 255–66; T. Naftali, L. Bar-Lev Schleider, I. Dotan, et al., “Cannabis Induces a Clinical Response in Patients with Crohn’s Disease: A Prospective Placebo-Controlled Study,” *Clinical Gastroenterology and Hepatology*

11, no. 10 (2013): 1276–80.

49. W. Ahmed and S. Katz, “Therapeutic Use of Cannabis in Inflammatory Bowel Disease,” *Gastroenterology and Hepatology* 12, no. 11 (2016): 668–79.

50. A. A. Izzo, F. Capasso, A. Costagliola, et al., “An Endogenous Cannabinoid Tone Attenuates Cholera Toxin-Induced Fluid Accumulation in Mice,” *Gastroenterology* 125, no. 3 (September 2003): 765–74, https://www.ncbi.nlm.nih.gov/pubmed/12949722.

51. Naftali et al., “Cannabis Induces.”

52. R. Schicho and M. Storr, “Alternative Targets within the Endocannabinoid System for Future Treatment of Gastrointestinal Diseases,” *Canadian Journal of Gastroenterology* 25, no. 7 (2011): 377–83.

53. J. Gotfried, R. Kataria, and R. Schey, “Review: The Role of Cannabinoids on Esophageal Function—What We Know Thus Far,” *Cannabis and Cannabinoid Research* 2, no. 1 (October 2017): 252–58, doi:10.1089/can.2017.0031.

54. LibertyPen, “Dr. Sanjay Gupta—Marijuana and Charlotte’s Web,” *YouTube*, November 1, 2013, https://www.youtube.com/watch?v=CiShwotFJR8.

55. L. D. Schurman and A. H. Lichtman, “Endocannabinoids: A Promising Impact for Traumatic Brain Injury,” *Frontiers in Pharmacology* 8 (2017): 69.

56. A. J. Hampson, M. Grimaldi, J. Axelrod, and D. Wink, “Cannabidiol and (-) Delta9-Tetrahydrocannabinol Are Neuroprotective Antioxidants,” *Proceedings of the National Academy of Sciences USA* 95, no. 14 (1998): 8268–73.

57. M. R. Pazos, N. Mohammed, H. Lafuente, et al., “Mechanisms of Cannabidiol Neuroprotection in Hypoxic-Ischemic Newborn Pigs: Role of 5HT(1)A and CB2 Receptors,” *Neuropharmacology* 71 (2013): 282–91; J. Fernández-Ruiz, M. A. Moro, and J. Martínez-Orgado, “Cannabinoids in Neurodegenerative Disorders and Stroke/Brain Trauma: From Preclinical Models to Clinical Applications,” *Neurotherapeutics* 12, no. 4 (2015): 793–806.

58. K. Hayakawa, K. Mishima, and M. Fujiwara, “Therapeutic Potential of Non-Psychotropic Cannabidiol in Ischemic Stroke,” *Pharmaceuticals* 3, no. 7 (2010): 2197–2212.

59. B. M. Nguyen, D. Kim, S. Bricker, et al., “Effect of Marijuana Use on Outcomes in Traumatic Brain Injury,” *American Surgeon* 80, no. 10 (October 2014): 979–83.

60. I. Lastres-Becker, F. Berrendero, J. J. Lucas, et al., “Loss of mRNA Levels, Binding and Activation of GTP-Binding Proteins for Cannabinoid CB1 Receptors in the Basal Ganglia of a Transgenic Model of Huntington’s Disease,” *Brain Research Journal* 929, no. 2 (March 2002): 236–42; O. Sagredo, M. R. Pazos, S. Valdeolivas, and J. Fernandez-Ruiz, “Cannabinoids: Novel Medicines for the Treatment of Huntington’s Disease,” *Recent Patents on CNS Drug Discovery* 7, no. 1 (2012): 41–48.

61. M. J. L. López-Sendón, G. Caldentey, T. Cubillo, et al., “A Double-Blind, Randomized, Cross-Over, Placebo-Controlled, Pilot Trial with Sativex in Huntington’s Disease,” *Journal of Neurology* 263, no. 7 (2016): 1390–1400.

62. S. Giacoppo, G. Mandolino, M. Galuppo, P. Bramanti, and E. Mazzon, “Cannabinoids: New Promising Agents in the Treatment of Neurological Diseases,” *Molecules*, 19, no. 11 (November 2014): 18781–816.

63. I. Lastres-Becker, H. H. Hansen, F. Berrendero, et al., “Alleviation of Motor Hyperactivity and Neurochemical Deficits by Endocannabinoid Uptake Inhibition in a Rat Model of Huntington’s Disease,” *Synapse* 44, no. 1 (April 2002): 23–35.

64. P. Consroe, J. Laguna, J. Allender, et al., “Controlled Clinical Trial of Cannabidiol in Huntington’s Disease,” *Pharmacology Biochemistry and Behavior* 40, no. 3 (November 1991): 701–8.

65. A. Curtis, I. Mitchell, S. Patel, N. Ives, and H. Rickards, “A Pilot Study Using Nabilone for

Symptomatic Treatment in Huntington's Disease," *Movement Disorders* 24, no. 15 (2009): 2254–59.

66. H. Wilms, L. Zecca, P. Rosenstiel, J. Sievers, G. Deuschl, and R. Lucius, "Inflammation in Parkinson's Diseases and Other Neurodegenerative Diseases: Cause and Therapeutic Implications," *Current Pharmaceutical Design* 13, no. 18 (2007): 1925–28.

67. I. Lastres-Becker and J. Fernandez-Ruiz, "An Overview of Parkinson's Disease and the Cannabinoid System and Possible Benefits of Cannabinoid-Based Treatments," *Current Medical Chemistry* 13, no. 30 (2006): 3705–18.

68. M. H. Chagas, A. W. Zuardi, V. Turnas, et al., "Effects of Cannabidiol in the Treatment of Patients with Parkinson's Disease: An Exploratory Double-Blind Trial," *Journal of Psychopharmacology* 28, no. 11 (November 2014): 1088–98, doi:10.1177/0269881114550355.

69. A. W. Zuardi, J. A. Crippa, J. E. Hallak, et al., "Cannabidiol for the Treatment of Psychosis in Parkinson's Disease," *Journal of Psychopharmacology* 23, no. 8 (November 2009): 979–83, doi:10.1177/0269881108096519.

70. Bradykinesia is the slow movement that is one of the hallmarks seen in Parkinson's disease. P. Consroe, R. Sandyk, and S. R. Snider, "Open Label Evaluation of Cannabidiol in Dystonic Movement Disorders," *International Journal of Neuroscience* 30, no. 4 (November 1986): 277–82.

71. B. G. Ramírez, C. Blázquez, T. Gómez del Pulgar, M. Guzmán, and M. L. de Ceballos, "Prevention of Alzheimer's Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation," *Journal of Neuroscience*: 25, no. 8 (February 23, 2005): 1904–13.

72. J. Koppel and P. Davies, "Targeting the Endocannabinoid System in Alzheimer's Disease," *Journal of Alzheimer's Disease* 15, no. 3 (2008): 495–504, doi:10.3233/JAD-2008-15315.

73. Ramírez et al., "Prevention of Alzheimer's Disease"; V. A. Campbell and A. Gowran, "Alzheimer's Disease: Taking the Edge Off with Cannabinoids?" *British Journal of Pharmacology* 152, no. 5 (2007): 655–62.

74. A. Shelef, Y. Barak, U. Berger, et al., "Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An Open Label, Add-On, Pilot Study," *Journal of Alzheimer's Disease* 51, no. 1 (2016): 15–19.

75. K. R. Müller-Vahl, H. Kolbe, U. Schneider, and H. M. Emrich, "Cannabinoids: Possible Role in Patho-Physiology and Therapy of Gilles de la Tourette Syndrome," *Acta Psychiatrica Scandinavica* 98, no. 6 (1998): 502–6, doi:10.1111/j.1600-0447.1998.tb10127.x.

76. B. S. Koppel, "Cannabis in the Treatment of Dystonia, Dyskinesias, and Tics," *Neurotherapeutics* 12, no. 4 (2015): 788–92, doi:10.1007/s13311-015-0376-4.

77. A. C. Campos and F. S. Guimarães, "Involvement of 5HT1A Receptors in the Anxiolytic-Like Effects of Cannabidiol Injected into the Dorsolateral Periaqueductal Gray of Rats," *Psychopharmacology* 199, no. 2 (2008): 223–30.

78. M. M. Bergamaschi, R. H. C. Queiroz, M. H. N. Chagas, et al., "Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients," *Neuropsychopharmacology* 36, no. 6 (May 2011): 1219–26, doi:10.1038/npp.2011.6.

79. E. Manrique-Garcia, S. Zammit, C. Dalman, T. Hemmingsson, and P. Allebeck, "Cannabis Use and Depression: A Longitudinal Study of a National Cohort of Swedish Conscripts," *BMC Psychiatry* 12, no. 112 (2012), doi:10.1186/1471-244x-12-112.

80. L. Grinspoon and J. B. Bakalar, "The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research," *Journal of Psychoactive Drugs* 30, no. 2 (April–June 1998): 171–77, doi:10.1080/02791072.1998.10399687.

81. R. Mechoulam, "Welcome and Keynote Speaker," CannMed Presentation, Boston, March 2016.

82. I. Akirav, “The Role of Cannabinoids in Modulating Emotional and Non-Emotional Memory Processes in the Hippocampus,” *Frontiers in Behavioral Neuroscience* 5 (2011): 34.

83. E. Ganon-Elazar and I. Akirav, “Cannabinoids Prevent the Development of Behavioral and Endocrine Alterations in a Rat Model of Intense Stress,” *Neuropsychopharmacology* 37 (August 2011), doi:10.1038/npp.2011.204.

84. C. Cameron, D. Watson, and J. Robinson, “Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumatic Stress Disorder–Related Insomnia and Nightmares, Chronic Pain, Harm Reduction, and Other Indications: A Retrospective Evaluation,” *Journal of Clinical Psychopharmacology* 34, no. 5 (2014): 559–64.

85. G. R. Greer, C. S. Grob, and A. L. Halberstadt, “PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program,” *Journal of Psychoactive Drugs* 46, no. 1 (January–March 2014): 73, doi:10.1080/02791072.2013.873843.

86. R. Jetly, A. Heber, G. Fraser, and D. Boisvert, “The Efficacy of Nabilone, a Synthetic Cannabinoid, in the Treatment of PTSD-Associated Nightmares: A Preliminary Randomized, Double-Blind, Placebo-Controlled Cross-Over Design Study,” *Psychoneuroendocrinology* 51 (January 2015): 585–88, doi:10.1016/j.psyneuen.2014.11.002.

87. G. Schwarcz and B. Karajgi, “Improvement in Refractory Psychosis with Dronabinol: Four Case Reports,” *Journal of Clinical Psychiatry* 71, no. 11 (November 2010): 1552–53.

88. B. C. McLoughlin, J. A. Pushpa-Rajah, D. Gillies, et al., “Cannabis and Schizophrenia,” *Cochrane Database of Systematic Reviews*, no. 10 (2014), Art. No.: CD004837.

89. S. Andréasson, P. Allebeck, A. Engström, and U. Rydberg, “Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts,” *Lancet* 330, no. 8574 (December 1987): 1483–86.

90. G. Schwarcz, B. Karajgi, and R. McCarthy, “Synthetic Delta-9-Tetrahydrocannabinol (Dronabinol) Can Improve the Symptoms of Schizophrenia,” *Journal of Clinical Psychopharmacology* 29, no. 3 (June 2009): 255–88, doi:10.1097/JCP.0b013e3181a6bc3b.

91. P. N. Surkin, S. L. Gallino, V. Luce, F. Correa, J. Fernandez-Solari, and A. De Laurentiis, “Pharmacological Augmentation of Endocannabinoid Signaling Reduces the Neuroendocrine Response to Stress,” *Psychoneuroendocrinology* 87 (January 2018): 131–40; M. Morena, S. Patel, J. S. Bains, and M. N. Hill, “Neurobiological Interactions between Stress and the Endocannabinoid System,” *Neuropsychopharmacology* 41, no. 1 (2015): 80–102, doi:10.1038/npp.2015.166; M. N. Hill and J. G. Tasker, “Endocannabinoid Signaling, Glucocorticoid-Mediated Negative Feedback, and Regulation of the Hypothalamic-Pituitary-Adrenal Axis,” *Neuroscience* 204 (March 1, 2012): 5–16; C. Grimaldi and A. Capasso, “Role of Lipid Rafts/Caveolae in the Anticancer Effect of Endocannabinoids,” *Mini-Reviews in Medicinal Chemistry* 12, no. 11 (2012): 1119–26.

92. M. Waldman, E. Hochhauser, M. Fishbein, D. Aravot, A. Shainberg, and Y. Sarne, “An Ultra-Low Dose of Tetrahydrocannabinol Provides Cardioprotection,” *Biochemical Pharmacology* 85, no. 11 (June 1, 2013): 1626–33, doi:10.1016/j.bcp.2013.03.014.

93. S. K. Walsh, C. Y. Hepburn, K. A. Kane, and C. L. Wainwright, “Acute Administration of Cannabidiol In Vivo Suppresses Ischaemia-Induced Cardiac Arrhythmias and Reduces Infarct Size When Given at Reperfusion,” *British Journal of Pharmacology* 160, no. 5 (July 2010): 1234–42.

94. Y. A. Shmist, I. Goncharov, M. Eichler, et al., “Delta-9-Tetrahydrocannabinol Protects Cardiac Cells from Hypoxia via CB2 Receptor Activation and Nitric Oxide Production,” *Molecular and Cellular Biochemistry* 283, nos. 1–2 (February 2006): 75–83.

95. E. A. Penner, H. Buettner, and M. A. Mittleman, “The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults,” *American Journal of Medicine* 126, no. 7 (July 2013): 583–89, doi:10.1016/j.amjmed.2013.03.002.

96. N. S. Chauhan, V. Sharma, V. K. Dixit, and M. Thakur, “A Review on Plants Used for

Improvement of Sexual Performance and Virility," *BioMed Research International* 2014 (2014): 868062.

97. A. J. Sun and M. L. Eisenberg, "Association between Marijuana Use and Sexual Frequency in the United States: A Population-Based Study," *Journal of Sexual Medicine* 14, no. 11 (November 2017): 1342–47.

98. K. J. Robinson, S. D. Twiss, N. Hazon, and P. P. Pomeroy, "Maternal Oxytocin Is Linked to Close Mother-Infant Proximity in Grey Seals (*Halichoerus grypus*)," *PLoS ONE* 10.12 (2015): e0144577.

99. C. T. Campbell, M. S. Phillips, and L. Manasco, "Cannabinoids in Pediatrics," *Journal of Pediatric Pharmacology and Therapeutics* 22, no. 3 (2017): 176–85.

100. Campbell, Phillips, and Manasco, "Cannabinoids in Pediatrics."

101. Di Marzo, Stella, and Zimmer, "Endocannabinoid Signalling."

CHAPTER 6

1. J. Sachs, E. McGlade, and D. Yurgelun-Todd, "Safety and Toxicology of Cannabinoids," *Neurotherapeutics* 12, no. 4 (2015): 735–46.

2. J. McPartland, "The Endocannabinoid System: An Osteopathic Perspective," *Journal of the American Osteopathic Association* 108, no. 10 (October 2008): 586–600, doi:10.7556/jaoa.2008.108.10.586.

3. Institute for Cannabis Therapeutics, "Additional Notes: Rescheduling of Cannabis," March 27, 2010, http://www.oregon.gov/pharmacy/imports/marijuana/staffreview/reschedulingcannabis-notes_3-10.pdf.

4. US Department of Justice, Drug Enforcement Administration, "Marijuana Rescheduling Petition, DEA Docket No. 86-22," September 6, 1988.

5. C. Sachse-Seeboth, J. Pfeil, D. Sehrt, et al., "Interindividual Variation in the Pharmacokinetics of Delta9-Tetrahydrocannabinol as Related to Genetic Polymorphisms in CYP2C9," *Clinical Pharmacology and Therapeutics* 85, no. 3 (March 2009): 273–76; K. Watanabe, S. Yamaori, T. Funahashi, T. Kimura, and I. Yamamoto, "Cytochrome P450 Enzymes Involved in the Metabolism of Tetrahydrocannabinols and Cannabinol by Human Hepatic Microsomes," *Life Sciences* 80, no. 15 (March 2007): 1415–19.

6. D. Van Booven, S. Marsh, H. McLeod, et al., "Cytochrome P450 2C9-CYP2C9," *Pharmacogenetics and Genomics* 20, no. 4 (2010): 277–81, doi:10.1097/FPC.0b013e3283349e84.

7. S. J. Heishman, M. A. Huestis, J. E. Henningfield, and E. J. Cone, "Acute and Residual Effects of Marijuana: Profiles of Plasma THC Levels, Physiological, Subjective, and Performance Measures," *Pharmacology Biochemistry and Behavior* 37, no. 3 (November 1990): 561–65, https://www.ncbi.nlm.nih.gov/pubmed/1965045.

8. R. L. Hartman and M. A. Huestis, "Cannabis Effects on Driving Skills," *Clinical Chemistry* 59, no. 3 (February 2013): 478–92, doi:10.1373/clinchem.2012.194381.

9. Insurance Institute for Highway Safety, *Status Report* 52, no. 4 (June 22, 2017).

10. J. D. Aydelotte, L. H. Brown, K. M. Luftman, et al., "Crash Fatality Rates after Recreational Marijuana Legalization in Washington and Colorado," *American Journal of Public Health* 107, no. 8 (August 1, 2017): 1329–31, doi:10.2105/AJPH.2017.303848.

11. R. Radhakrishnan, S. T. Wilkinson, and D. C. D'Souza, "Gone to Pot: A Review of the Association between Cannabis and Psychosis," *Frontiers in Psychiatry* 5 (2014): 54.

12. M. Backes and A. Weil, *Cannabis Pharmacy: The Practical Guide to Medical Marijuana*, rev. and updated (New York: Black Dog and Leventhal, 2017).

13. S. E. M. Lewis, C. Rapino, M. Di Tommaso, et al., “Differences in the Endocannabinoid System of Sperm from Fertile and Infertile Men,” *PLoS One* 7, no. 10 (2012): e47704; S. S. Du Plessis, A. Agarwal, and A. Syriac, “Marijuana, Phytocannabinoids, the Endocannabinoid System, and Male Fertility,” *Journal of Assisted Reproduction and Genetics* 32, no. 11 (2015): 1575–88; L. E. Hollister, “Interactions of Cannabis with Other Drugs in Man,” *NIDA Research Monograph* 68 (1986):110–16.

14. M. Maccarrone, H. Valensise, M. Bari, N. Lazzarin, C. Romanini, and A. Finazzi-Agrò, “Relation between Decreased Anandamide Hydrolase Concentrations in Human Lymphocytes and Miscarriage,” *Lancet* 355, no. 9212: 1326–29.

15. S. J. Brown, F. K. Mensah, J. A. Kit, et al., “Use of Cannabis during Pregnancy and Birth Outcomes in an Aboriginal Birth Cohort: A Cross-Sectional, Population-Based Study,” *BMJ Open* 6, no. 2 (2016): e010286.

16. S. N. Conner, E. B. Carter, M. G. Tuuli, G. A. Macones, and A. G. Cahill, “Maternal Marijuana Use and Neonatal Morbidity,” *American Journal of Obstetrics and Gynecology* 213, no. 3 (September 2015): 422.e1–4.

17. K. C. Chabarria, D. A. Racusin, K. M. Antony, et al., “Marijuana Use and Its Effects in Pregnancy,” *American Journal of Obstetrics and Gynecology* 215, no. 4 (October 2016): 506.e1–7.

18. J. C. A. Lacson, J. D. Carroll, E. Tuazon, E. J. Castelao, L. Bernstein, and V. K. Cortessis, “Population-Based Case-Control Study of Recreational Drug Use and Testis Cancer Risk Confirms Association between Marijuana Use and Non-Seminoma Risk,” *Cancer* 118, no. 21 (2012): 5374–83.

19. J. Gurney, C. Shaw, J. Stanley, V. Signal, and D. Sarfati, “Cannabis Exposure and Risk of Testicular Cancer: A Systematic Review and Meta-Analysis,” *BMC Cancer* 15 (2015): 897, https://doi.org/10.1186/s12885-015-1905-6; R. C. Callaghan, P. Allebeck, O. Akre, K. A. McGlynn, and A. Sidorchuk, “Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011,” *Cancer Epidemiology, Biomarkers and Prevention* 26, no. 11 (November 2017): 1644–52, doi:10.1158/1055-9965.EPI-17-0428.

20. C. S. Breivogel, S. M. Scates, I. O. Beletskaya, O. B. Lowery, M. D. Aceto, and B. R. Martin, “The Effects of Delta9-Tetrahydrocannabinol Physical Dependence on Brain Cannabinoid Receptors,” *European Journal of Pharmacology* 459, nos. 2–3 (January 17, 2003): 139–50.

21. C. Mokrysz, R. Landy, S. H. Gage, M. R. Munafò, J. P. Rosier, and H. V. Curran, “Are IQ and Educational Outcomes in Teenagers Related to Their Cannabis Use? A Prospective Cohort Study,” *Journal of Psychopharmacology* 30, no. 2 (2016): 159–68, doi:10.1177/0269881115622241.

22. J. C. Scott, S. T. Slomiak, J. D. Jones, et al., “Association of Cannabis with Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis,” *JAMA Psychiatry* (April 2018), doi:10.1001/jamapsychiatry.2018.0335.

23. Committee on Substance Abuse, Committee on Adolescence, “The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update,” *Pediatrics* 135, no. 3 (March 2015), http://pediatrics.aappublications.org/content/135/3/584.

24. L. L. Iversen, *The Science of Marijuana* (New York: Oxford University Press, 2008), 95–96.

25. A. Hughes, R. N. Lipar, and M. Williams, “State Estimates of Adolescent Marijuana Use and Perceptions of Risk of Harm from Marijuana Use: 2013 and 2014,” *CBHSQ Report*, December 17, 2015, https://www.samhsa.gov/data/sites/default/files/report_2121/ShortReport-2121.html.

26. Colorado Department of Public Health and Environment, “Marijuana Use among Youth in

Colorado: Healthy Kids Colorado Survey 2015," https://www.colorado.gov/pacific/sites/default/files/PF_Youth_HKCS_MJ-Infographic-Digital.pdf.

27. N. D. Volkow, "Marijuana's Lasting Effects on the Brain," *National Institute on Drug Abuse*, March 2013, https://www.drugabuse.gov/about-nida/directors-page/messages-director/2012/09/marijuanas-lasting-effects-brain.

28. J. Stiles and T. L. Jernigan, "The Basics of Brain Development," *Neuropsychology Review* 20, no. 4 (December 2010): 327–48.

29. A. Zalesky, N. Solowij, M. Yücel, et al., "Effect of Long-Term Cannabis Use on Axonal Fibre Connectivity," *Brain* 135, pt. 7 (July 2012): 2245–55, doi:10.1093/brain/aws136; F. M. Filbey, S. Aslan, V. D. Calhoun, et al., "Long-Term Effects of Marijuana Use on the Brain," *Proceedings of the National Academy of Sciences USA* 111, no. 47 (November 2014): 16913–18, doi:10.1073/pnas.1415297111; K. M. Lisdahl, N. E. Wright, C. Kirchner-Medina, K. E. Maple, and S. Shollenbarger, "Considering Cannabis: The Effects of Regular Cannabis Use on Neurocognition in Adolescents and Young Adults," *Current Addiction Reports* 1 (2014): 144–56; T. Demirakca, A. Sartorius, G. Ende, et al., "Diminished Gray Matter in the Hippocampus of Cannabis Users: Possible Protective Effects of Cannabidiol," *Drug and Alcohol Dependency* 114 (2011): 242–45.

30. J. M. Gilman, J. K. Kuster, S. Lee, et al., "Cannabis Use Is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users," *Journal of Neuroscience* 34, no. 16 (April 2014): 5529–38, doi:10.1523/JNEUROSCI.4745-13.2014.

31. B. J. Weiland, R. E. Thayer, B. E. Depue, A. Sabbineni, A. D. Bryan, and K. E. Hutchison, "Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults," *Journal of Neuroscience* 35, no. 4 (January 28, 2015): 1505–12; G. Z. Tau and B. S. Peterson, "Normal Development of Brain Circuits," *Neuropsychopharmacology Reviews* 35 (2010): 147–68.

32. P. van der Pol, N. Liebregts, R. de Graaf, et al., "Mental Health Differences between Frequent Cannabis Users with and without Dependence and the General Population," *Addiction* 108, no. 8 (2013): 1459–69.

33. Watanabe et al., "Cytochrome P450 Enzymes."

34. R. Jiang, S. Yamaori, S. Takeda, I. Yamamoto, and K. Watanabe, "Identification of Cytochrome P4540 Enzymes Responsible for Metabolism of Cannabidiol by Human Liver Microsomes," *Life Sciences* 89, nos. 5–6 (August 2011): 165–70, doi:10.1016/j.lfs.2011.05.018.

35. Trustees of Indiana University, "The Flockhart Table," http://medicine.iupui.edu/clinpharm/ddis/clinical-table.

36. S. M. Stout and N. M. Cimino, "Exogenous Cannabinoids as Substrates, Inhibitors, and Inducers of Human Drug Metabolizing Enzymes: A Systematic Review," *Drug Metabolism Reviews* 46 (2014): 86–95.

37. Realm of Caring, "AED Potential Interactions with CBD," https://theroc.us/images/aedinteractions.pdf.

38. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5th ed. (Arlington, VA: American Psychiatric Association, 2013).

39. D. S. Timberlake, "A Comparison of Drug Use and Dependence between Blunt Smokers and Other Cannabis Users," *Substance Use and Misuse* 44, no. 3 (2009): 401–15, doi:10.1080/10826080802347651.

40. F. Cascini, C. Aiello, and G. Di Tanna, "Increasing Delta-9-Tetrahydrocannabinol (Δ-9-THC) Content in Herbal Cannabis over Time: Systematic Review and Meta-Analysis," *Current Drug Abuse Reviews* 5, no. 1 (March 2012): 32–40.

41. N. L. Benowitz and J. E. Henningfield, "Establishing a Nicotine Threshold for Addiction,"

New England Journal of Medicine 331, no. 2 (1994): 123–25.

42. J. Graham, M. Barberio, and G. S. Wang, “Capsaicin Cream for Treatment of Cannabinoid Hyperemesis Syndrome in Adolescents: A Case Series,” *Pediatrics* 140, no. 6 (November 2017): e20163795, doi: 10.1542/peds.2016-3795.

CHAPTER 8

1. D. Piomelli and E. B. Russo, “The *Cannabis sativa* versus *Cannabis indica* Debate: An Interview with Ethan Russo, MD,” *Cannabis and Cannabinoid Research* 1, no. 1 (2016): 44–46.

2. Releaf App, https://releafapp.com/about-us.

3. L. I. Rebeiro and P. W. Ind, “Effect of Cannabis Smoking on Lung Function and Respiratory Symptoms: A Structured Literature Review,” *NPJ: Primary Care Respiratory Medicine* 16071 (2016).

4. R. C. Callaghan, P. Allebeck, and A. Sidorchuk, “Marijuana Use and Risk of Lung Cancer: A 40-Year Cohort Study,” *Cancer Causes and Control* 24, no. 10 (October 2013): 1811–20; M. Joshi, A. Joshi, and T. Bartter, “Marijuana and Lung Diseases,” *Current Opinion in Pulmonary Medicine* 20, no. 2 (March 2014): 173–79.

5. B. Wilsey, T. Marcotte, R. Deutsch, B. Gouaux, S. Sakai, and H. Donaghe, “Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain,” *Journal of Pain* 14, no. 2 (2013): 136–48.

CHAPTER 10

1. A. J. Hampson, M. Grimaldi, J. Axelrod J, and D. Wink, “Cannabidiol and (-) Delta9-Tetrahydrocannabinol Are Neuroprotective Antioxidants,” *Proceedings of the National Academy of Science* 95, no. 14 (1998): 8268–73.

2. G. Gruden, F. Barutta, G. Kunos, and P. Pacher, “Role of the Endocannabinoid System in Diabetes and Diabetic Complications,” *British Journal of Pharmacology* 173, no. 7 (2016): 1116–27.

3. R. Durst, H. Danenberg, R. Gallily, et al., “Cannabidiol, a Nonpsychoactive *Cannabis* Constituent, Protects against Myocardial Ischemic Reperfusion Injury,” *American Journal of Physiology: Heart and Circulatory Physiology* 293, no. 6 (December 2007): H3602–7; Y. Feng, F. Chen, and Q. Xia, “Pharmacologic Effects of Cannabidiol on Acute Reperfused Myocardial Infarction in Rabbits: Evaluated 3.0T Cardiac Magnetic Resonance Imaging and Histopathology,” *Journal of Cardiovascular Pharmacology* 66, no. 4 (October 2015): 354–63.

4. R. Linge, L. Jiménez-Sánchez, L. Campa, et al., “Cannabidiol Induces Rapid-Acting Antidepressant-Like Effects and Enhances Cortical 5-HT/Glutamate Neurotransmission: Role of 5-HT1A Receptors,” *Neuropharmacology* 103 (2016): 16–26.

5. S. Takeda, K. Misawa, I. Yamamoto, and K. Watanabe, “Cannabidiolic Acid as a Selective Cyclooxygenase-2 Inhibitory Component in Cannabis,” *Drug Metabolism and Disposition* 36, no. 9 (September 2008): 1917–21, http://doi.org/10.1124/dmd.108.020909.

6. M. O. Bonn-Miller, M. J. E. Loflin, B. F. Thomas, J. P. Marcu, T. Hyke, and R. Vandrey, “Labeling Accuracy of Cannabidiol Extracts Sold Online,” *Journal of the American Medical Association* 318, no. 17 (2017): 1708–9, doi:10.1001/jama.2017.11909.

CHAPTER 11

1. E. B. Russo, “Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes,” *Cannabis and Cannabinoid Research* 1, no. 1 (2016): 154–65, doi:10.1089/can.2016.0009.

2. V. Di Marzo and I. Matias, “Endocannabinoid Control of Food Intake and Energy Balance,” *Nature Neuroscience* 8 (2005): 585–89.

3. A. R. Alvheim, M. K. Malde, D. Osei-Hyiaman, et al., “Dietary Linoleic Acid Elevates Endogenous 2-AG and Anandamide and Induces Obesity,” *Obesity* 20 (2012): 1984–94.

4. A. P. Simopoulos, “The Importance of the Ratio of Omega-6/Omega-3 Essential Fatty Acids,” *Biomedicine and Pharmacotherapy* 56, no. 8 (October 2002): 365–79.

5. R. L. Carr, A. Borazjani, and M. K. Ross, “Effect of Developmental Chlorpyrifos Exposure, on Endocannabinoid Metabolizing Enzymes, in the Brain of Juvenile Rats,” *Toxicological Sciences* 122 (2011): 112–20; C. B. Quistad, S. E. Sparks, and J. E. Casida, “Fatty Acid Amide Hydrolase Inhibition by Neurotoxic Organophosphorus Pesticides,” *Toxicology and Applied Pharmacology* 173 (2001): 48–55.

6. L. Chen, J. Zhang, F. Li, et al., “Endogenous Anandamide and Cannabinoid Receptor-2 Contribute to Electroacupuncture Analgesia in Rats,” *Journal of Pain* 10 (2009): 732–39.

7. N. A. Darmani, A. A. Izzo, B. Degenhardt, et al., “Involvement of the Cannabimimetic Compound, N-Palmitoyl-Ethanolamine, in Inflammatory and Neuropathic Conditions: Review of the Available Pre-Clinical Data, and First Human Studies,” *Neuropharmacology* 48 (2005): 1154–63.

8. J. McPartland, G. Guy, and V. DiMarzo, “Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions That Upregulate the Endocannabinoid System,” edited by A. A. Romanovsky, *PLoS ONE* 9, no. 3 (2014): e89566, doi:10.1371/journal.pone.0089566.

APPENDIX

1. Evidence-Based Medicine Consult, “Substrates—Cytochrome P450 (CYP) Enzymes Drug Table,” https://www.ebmconsult.com/content/pages/cytochrome-cyp-p450-enzyme-medication-herbs-substrates.

Works Cited

Abel, E. L. “Cannabis in the Ancient World.” In *Marihuana: The First Twelve Thousand Years*. New York City: Plenum, 1980.

Abrams, D. I. “Integrating Cannabis into Clinical Cancer Care.” *Current Oncology* 23, suppl. 2 (March 2016): S8–14.

Abrams, D. I., P. Couey, S. B. Shade, M. E. Kelly, and N. L. Benowitz. “Cannabinoid-Opioid Interaction in Chronic Pain.” *Clinical Pharmacology and Therapeutics* 90, no. 6 (December 2011): 844–51. doi:10.1038/clpt.2011.

Abu ‘Ali al-Husayn ibn Sina. *The Canon of Medicine*. 1025.

Adams, C. “The Man behind the Marijuana Ban for All the Wrong Reasons.” *CBS News*. November 17, 2016. https://www.cbsnews.com/news/harry-anslinger-the-man-behind-the-marijuana-ban.

Agenda.ge. “Court Abolishes Imprisonment for Sowing of Cannabis for Personal Use.” July 14, 2017. https://agenda.ge/news/83501/eng.

Ahmed, W., and S. Katz. “Therapeutic Use of Cannabis in Inflammatory Bowel Disease.” *Gastroenterology and Hepatology* 12, no. 11 (2016): 668–79.

Akirav, I. “The Role of Cannabinoids in Modulating Emotional and Non-Emotional Memory Processes in the Hippocampus.” *Frontiers in Behavioral Neuroscience* 5 (2011): 34.

Alabama State Legislature, House Bill 61, 2016, https://legiscan.com/AL/text/HB61/2016.

Alvheim, A. R., M. K. Malde, D. Osei-Hyiaman, et al. “Dietary Linoleic Acid Elevates Endogenous 2-AG and Anandamide and Induces Obesity.” *Obesity* 20 (2012): 1984–94.

American Academy of Pain Medicine. “AAPM Facts and Figures on Pain.” http://www.painmed.org/PatientCenter/Facts_on_Pain.aspx.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. Arlington, VA: American Psychiatric Association, 2013.

Americans for Safe Access. “Kentucky Legal Information.” http://www.safeaccessnow.org/kentucky_legal_information.

Andre, C. M. “*Cannabis sativa*: ‘The Plant of the Thousand and One Molecules.” *Frontiers in Plant Science* 7 (2016): 19. doi:10.3389/fpls.2016.00019.

Andréasson, S., P. Allebeck, A. Engström, and U. Rydberg. “Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts.” *Lancet* 330, no. 8574 (December 1987): 1483–86.

Appendino, G., S. Gibbons, A. Giana, et al. “Antibacterial Cannabinoids from *Cannabis sativa*: A Structure-Activity Study.” *Journal of Natural Products* 71, no. 8 (August 2008): 1427–30. doi: 10.1021/np8002673.

Arnold, M. “Greece Moves Forward on Legalizing Medical Use.” *Cannabis Industry Journal*. January 23, 2018. https://www.cannabisindustryjournal.com/news_article/greece-moves-forward-on-legalizing-medical-use.

Associated Press. “Colombian President Signs Decree to Legalise Medical Marijuana.” *Guardian*, December 22, 2015. https://www.theguardian.com/world/2015/dec/22/colombia-president-legalise-medical-marijuana.

Attanasio, C. “Chile Marijuana Legalization: Michelle Bachelet Removes Weed from ‘Hard Drug’ List, Approves Medical Pot.” *Latin Times*, December 7, 2015. http://www.latintimes.com/chile-marijuana-legalization-michelle-bachelet-removes-weed-hard-drug-list-approves-357337.

Australian Associated Press. “Australia Aims to Be World’s Top Medicinal Cannabis Supplier after

Exports Get Green Light." *Guardian*, January 3, 2018. https://www.theguardian.com/society/2018/jan/04/australia-aims-to-be-worlds-top-medicinal-cannabis-supplier-after-exports-get-green-light.

Aydelotte, J. D., L. H. Brown, K. M. Luftman, et al. "Crash Fatality Rates after Recreational Marijuana Legalization in Washington and Colorado." *American Journal of Public Health* 107, no. 8 (August 1, 2017): 1329–31. doi:10.2105/AJPH.2017.303848.

Bachhuber, M. A., B. Saloner, C. O. Cunningham, and C. L. Barry. "Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010." *JAMA: Internal Medicine* 174, no. 10 (2014): 1668–73. doi:10.1001/jamainternmed.2014.4005.

Backes, M., and A. Weil. *Cannabis Pharmacy: The Practical Guide to Medical Marijuana*. Rev. and updated. New York: Black Dog and Leventhal, 2017.

Barreiro, R. "Argentina Gives Green Light to Use of Medical Marijuana." *El País*, March 30, 2017. https://elpais.com/elpais/2017/03/30/inenglish/1490870431_851473.html.

Baum, D. "Legalize It All: How to Win the War on Drugs." *Harper's Bazaar* (April 2016).

BDO, "Newsletter: Medical Cannabis in Puerto Rico and Taxation," August 11, 2017, http://www.bdopr.com/en-gb/insights/tax/tax-alert/medical-cannabis-inpuerto-rico-and-taxation.

Benowitz, N. L., and J. E. Henningfield. "Establishing a Nicotine Threshold for Addiction." *New England Journal of Medicine* 331, no. 2 (1994): 123–25.

Ben-Shabat, S., E. Fride, T. Sheskin, et al. "An Entourage Effect: Inactive Endogenous Fatty Acid Glycerol Esters Enhance 2-Arachidonoyl-Glycerol Cannabinoid Activity." *European Journal of Pharmacology* 353, no. 1 (1998): 23–31.

Berg, S. "Norway." *International Association for Cannabinoid Medicines*. July 28, 2014. https://www.cannabis-med.org/index.php?tpl=page&id=289&lng=en.

Bergamaschi, M. M., R. H. C. Queiroz, M. H. N. Chagas, et al. "Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients." *Neuropsychopharmacology* 36, no. 6 (May 2011): 1219–26. doi:10.1038/npp.2011.6.

Berger, A., G. Crozier, and T. Bisogno. "Anandamide and Diet: Inclusion of Dietary Arachidonate and Docosahexaenoate Leads to Increased Brain Levels of the Corresponding *N*-Acylethanolamines in Piglets." *National Academy of Sciences* 98, no. 11 (May 2001): 6402–6.

Blázquez, C., A. Carracedo, L. Barrado, et al. "Cannabinoid Receptors as Novel Targets for the Treatment of Melanoma." *FASEB Journal* 20 (2006): 2633–35.

Blázquez, C., L. González-Feria, L. Álvarez, A. Haro, M. L. Casanova, and M. Guzmán. "Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas." *Cancer Research* 64, no. 16 (August 15, 2004): 5617–23. doi:10.1158/0008-5472.CAN-03-3927.

Bonn-Miller, M. O., M. J. E. Loflin, B. F. Thomas, J. P. Marcu, T. Hyke, and R. Vandrey. "Labeling Accuracy of Cannabidiol Extracts Sold Online." *Journal of the American Medical Association* 318, no. 17 (2017): 1708–9. doi:10.1001/jama.2017.11909.

Booker, Cory: United States Senator for New Jersey. "Lawmakers Reintroduce Bipartisan, Bicameral Medical Marijuana Bill." June 15, 2017. https://www.booker.senate.gov/?p=press_release&id=613.

Booth, J. K., J. E. Page, and J. Bohlmann. "Terpene Synthases from *Cannabis sativa*." *PLoS One* 12, no. 3 (March 2017): e0173911. doi:10.1371/journal.pone.0173911.

Booth, M. *Cannabis: A History*. New York: St. Martin's Press, 2003.

Booz, G. W. "Cannabidiol as an Emergent Therapeutic Strategy for Lessening the Impact of Inflammation on Oxidative Stress." *Free Radical Biology and Medicine* 51, no. 5 (2011): 1054–61.

Breivogel, C. S., S. M. Scates, I. O. Beletskaya, O. B. Lowery, M. D. Aceto, and B. R. Martin. "The Effects of Delta9-Tetrahydrocannabinol Physical Dependence on Brain Cannabinoid Receptors." *European Journal of Pharmacology* 459, nos. 2–3 (January 17, 2003): 139–50.

Brenneisen, R. "Chemistry and Analysis of Phytocannabinoids and Other Cannabis Constituents." In *Marijuana and the Cannabinoids*, edited by M. A. ElSohly (Totowa, NJ: Humana Press, 1984).

Brown, S. J., F. K. Mensah, J. A. Kit, et al. “Use of Cannabis during Pregnancy and Birth Outcomes in an Aboriginal Birth Cohort: A Cross-Sectional, Population-Based Study.” *BMJ Open* 6, no. 2 (2006): e010286.

Bud, M. “Texas to Roll Out First CBD Sales by End of Year.” *Marijuana.com*. November 27, 2017. https://www.marijuana.com/news/2017/11/texas-to-roll-out-first-cbd-sales-by-end-of-year.

Cabral, G. A. “Marijuana and Cannabinoids: Effects on Infections, Immunity and AIDS.” *Journal of Cannabis Therapeutics* 1 (2001): 61–85.

Calignano, A., G. La Rana, A. Giuffrida, and D. Piomelli. “Control of Pain Initiation by Endogenous Cannabinoids.” *Nature* 394 (1998): 277–81.

Callaghan, R. C., P. Allebeck, O. Akre, K. A. McGlynn, and A. Sidorchuk. “Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011.” *Cancer Epidemiology, Biomarkers and Prevention* 26, no. 11 (November 2017): 1644–52. doi:10.1158/1055-9965.EPI-17-0428.

Callaghan, R. C., P. Allebeck, and A. Sidorchuk. “Marijuana Use and Risk of Lung Cancer: A 40-Year Cohort Study.” *Cancer Causes and Control* 24, no. 10 (October 2013): 1811–20.

Cameron, C., D. Watson, and J. Robinson. “Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumatic Stress Disorder–Related Insomnia and Nightmares, Chronic Pain, Harm Reduction, and Other Indications: A Retrospective Evaluation.” *Journal of Clinical Psychopharmacology* 34, no. 5 (2014): 559–64.

Campbell, Christopher T., Marjorie Shaw Phillips, and Kalen Manasco. “Cannabinoids in Pediatrics.” *Journal of Pediatric Pharmacology and Therapeutics* 22, no. 3 (May–June 2017): 176–85.

Campbell, V. A., and A. Gowran. “Alzheimer’s Disease: Taking the Edge Off with Cannabinoids?” *British Journal of Pharmacology* 152, no. 5 (2007): 655–62.

Campos, A. C., and F. S. Guimarães. “Involvement of 5HT1A Receptors in the Anxiolytic-Like Effects of Cannabidiol Injected into the Dorsolateral Periaqueductal Gray of Rats.” *Psychopharmacology* 199, no. 2 (2008): 223–30.

CARERS Act of 2017. S. 1764. 115th Cong. (2017). https://www.congress.gov/bill/115th-congress/senate-bill/1764/cosponsors?overview=closed#tabs.

Carothers, W. H. Linear Polyamides and Their Production. US Patent 2130523A. September 20, 1938. https://www.google.com/patents/US2130523.

Carr, R. L., A. Borazjani, and M. K. Ross. “Effect of Developmental Chlorpyrifos Exposure, on Endocannabinoid Metabolizing Enzymes, in the Brain of Juvenile Rats.” *Toxicological Sciences* 122 (2011): 112–20.

Carracedo, A., M. Gironella, M. Lorente, et al. “Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress-Related Genes.” *Cancer Research* 66, no. 3 (2006): 6748–55.

Cascini F, C. Aiello, and G. Di Tanna. “Increasing Delta-9-Tetrahydrocannabinol (Δ-9-THC) Content in Herbal Cannabis over Time: Systematic Review and Meta-Analysis.” *Current Drug Abuse Reviews* 5, no. 1 (March 2012): 32–40.

Castellano, C., C. Rossi-Arnaud, V. Cestari, and M. Costanzi. “Cannabinoids and Memory: Animal Studies.” *Current Drug Targets: Central Nervous System and Neurological Disorders* 2 (2003): 389–402.

Center for Substance Abuse Research. “Heroin.” October 29, 2013. http://www.cesar.umd.edu/cesar/drugs/heroin.asp.

Centers for Disease Control and Prevention. “New Research Reveals the Trends and Risk Factors behind America’s Growing Heroin Epidemic.” July 7, 2015. https://www.cdc.gov/media/releases/2015/p0707-heroin-epid.

Chabarria, K. C., D. A. Racusin, K. M. Antony, et al. “Marijuana Use and Its Effects in Pregnancy.” *American Journal of Obstetrics and Gynecology* 215, no. 4 (October 2016): 506.e1–7.

Chagas, M. H., A. W. Zuardi, V. Turnas, et al. “Effects of Cannabidiol in the Treatment of Patients

with Parkinson's Disease: An Exploratory Double-Blind Trial." *Journal of Psychopharmacology* 28, no. 11 (November 2014): 1088–98. doi:10.1177/0269881114550355.
Chakrabarti, B., A. Persico, N. Battista, and M. Maccarrone. "Endocannabinoid Signaling in Autism." *Neurotherapeutics* 12, no. 4 (2015): 837–47.
Chakravarti, B., J. Ravi, and R. K. Ganju. "Cannabinoids as Therapeutic Agents in Cancer: Current Status and Future Implications." *Oncotarget* 5, no. 15 (2014): 5852–72.
Chaperon, F., and M.-H. Thiébot. "Behavioral Effects of Cannabinoid Agents in Animals." *Critical Reviews in Neurobiology* 13 (1999): 243–81.
Chauhan, N. S., V. Sharma, V. K. Dixit, and M. Thakur. "A Review on Plants Used for Improvement of Sexual Performance and Virility." *BioMed Research International* 2014 (2014): 868062.
Chen, L., J. Zhang J., F. Li, et al. "Endogenous Anandamide and Cannabinoid Receptor-2 Contribute to Electroacupuncture Analgesia in Rats." *Journal of Pain* 10 (2009): 732–39.
Christensen, D. L., J. Baio, K. Van Naarden Braun, et al. "Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012." *Morbidity and Mortality Weekly Report* 65, no. 3 (April 1, 2016): 1–23.
Clarke, R. C., and D. P. Watson. "Cannabis and Natural Cannabis Medicines." In *Marijuana and the Cannabinoids*, edited by M. A. ElSohly (Totowa, NJ: Humana Press, 1984).
Cole, J. M. "Memorandum for all United States Attorneys: Guidance Regarding Marijuana Enforcement." April 29, 2013. https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf.
Committee on Substance Abuse, Committee on Adolescence. "The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update." *Pediatrics* 135, no. 3 (March 2015). http://pediatrics.aappublications.org/content/135/3/584.
Conner, S. N., E. B. Carter, M. G. Tuuli, G. A. Macones, and A. G. Cahill. "Maternal Marijuana Use and Neonatal Morbidity." *American Journal of Obstetrics and Gynecology* 213, no. 3 (September 2015): 422.e1–4.
Consroe, P., J. Laguna, J. Allender, et al. "Controlled Clinical Trial of Cannabidiol in Huntington's Disease." *Pharmacology Biochemistry and Behavior* 40, no. 3 (November 1991): 701–8.
Consroe, P., R. Sandyk, and S. R. Snider. "Open Label Evaluation of Cannabidiol in Dystonic Movement Disorders." *International Journal of Neuroscience* 30, no. 4 (November 1986): 277–82.
Controlled Substances Act. 2 U.S.C., Section 801 (a), 811, 812.
Costiniuk, C. T., E. Mills, and C. L. Cooper. "Evaluation of Oral Cannabinoid-Containing Medications for the Management of Interferon and Ribavirin-Induced Anorexia, Nausea and Weight Loss in Patients Treated for Chronic Hepatitis C Virus." *Canadian Journal of Gastroenterology and Hepatology* 22, no. 4 (April 2008): 376–80.
Crowell, P. L., C. E. Elson, H. H. Bailey, A. Elegbede, J. D. Haag, and M. N. Gould. "Human Metabolism of the Experimental Cancer Therapeutic Agent D-Limonene." *Cancer Chemotherapy Pharmacology* 35, no. 1 (1994): 31–37. https://www.ncbi.nlm.nih.gov/pubmed/7987974.
"Cultivation of Cannabis for Medicinal Purposes Is Legal in Zambia—Home Affairs Minister." *Lusaka Times*, March 2, 2017. https://www.lusakatimes.com/2017/03/02/cultivation-cannabis-medicinal-purposes-legal-zambia-home-affairs-minister.
Curtis, A., I. Mitchell, S. Patel, N. Ives, and H. Rickards. "A Pilot Study Using Nabilone for Symptomatic Treatment in Huntington's Disease." *Movement Disorders* 24, no. 15 (2009): 2254–59.
Dach, J., E. A. Moore, and J. Kander. *Cannabis Extracts in Medicine*. Jefferson, NC: McFarland, 2015.
Darmani, N. A., A. A. Izzo, B. Degenhardt, et al. "Involvement of the Cannabimimetic Compound, N-Palmitoyl-Ethanolamine, in Inflammatory and Neuropathic Conditions: Review of the

Available Pre-Clinical Data, and First Human Studies." *Neuropharmacology* 48 (2005): 1154–63.
Demirakca, T., A. Sartorius, G. Ende, et al. "Diminished Gray Matter in the Hippocampus of Cannabis Users: Possible Protective Effects of Cannabidiol." *Drug and Alcohol Dependence* 114 (2011): 242–45.
De Petrocellis, L., A. Ligresti, A. S. Moriello, et al. "Effects of Cannabinoids and Cannabinoid-Enriched *Cannabis* Extracts on TRP Channels and Endocannabinoid Metabolic Enzymes." *British Journal of Pharmacology* 163, no. 7 (2011): 1479–94.
De Petrocellis, L., P. Orlando, A. S. Moriello, et al. "Cannabinoid Actions at TRPV Channels: Effects on TRPV3 and TRPV4 and Their Potential Relevance to Gastrointestinal Inflammation." *Acta Physiologica* 204, no. 2 (February 2012): 255–66.
Department of Health and Human Services, "Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health." *Substance Abuse and Mental Health Services Administration*. December 2015, https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.
Department of Justice, Drug Enforcement Administration. "Schedules of Controlled Substances: Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [D-9-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules from Schedule II to Schedule III." *Federal Register* 64, no. 127 (July 2, 1999): 35928–30.
Depino, A. M. "Peripheral and Central Inflammation in Autism Spectrum Disorders." *Molecular and Cellular Neuroscience* 53 (March 2013): 69–76.
Devane, W. A., L. Hanus, A. Breuer, et al. "Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor." *Science* 258 (1992): 1946–49.
Devinsky, O., M. R. Cilio, H. Cross, et al. "Cannabidiol: Pharmacology and Potential Therapeutic Role in Epilepsy and Other Neuropsychiatric Disorders." *Epilepsia* 55, no. 6 (2014): 791–802.
Diario Oficial de la Federación. "Decreto Por el Que se Reforman y Adicionan Diversas Disposiciones de la Ley General de Salud y del Código Penal Federal." June 19, 2017. http://www.dof.gob.mx/nota_detalle.php?codigo=5487335&fecha=19/06/2017.
Di Marzo, V., M. Côté, I. Matias, et al. "Changes in Plasma Endocannabinoid Levels in Viscerally Obese Men Following a 1-Year Lifestyle Modification Programme and Waist Circumference Reduction: Associations with Changes in Metabolic Risk Factors." *Diabetologia* 52, no. 2 (February 2009): 213–17. doi:10.1007/s00125-008-1178-6.
Di Marzo, V., A. Fontana, H. Cadas, et al. "Formation and Inactivation of Endogenous Cannabinoid Anandamide in Central Neurons." *Nature* 372 (1994): 686–91.
Di Marzo, V., and I. Matias. "Endocannabinoid Control of Food Intake and Energy Balance." *Nature Neuroscience* 8 (2005): 585–89.
Di Marzo, V., D. Melck, T. Bisogno, and L. De Petrocellis. "Endocannabinoids: Endogenous Cannabinoid Receptor Ligands with Neuromodulatory Action." *Trends in Neurosciences* 21, no. 12 (December 1998): 521–28.
Di Marzo, V., N. Stella, and A. Zimmer. "Endocannabinoid Signalling and the Deteriorating Brain." *Nature Neuroscience* 16, no. 1 (2015): 30–42.
Dinh, T. P., D. Carpenter, F. M. Leslie, et al. "Brain Monoglyceride Lipase Participating in Endocannabinoid Inactivation." *Proceedings of the National Academy of Sciences of the United States of America* 99, no. 16 (August 2002): 10819–24.
Doward, J. "Legal Marijuana Cuts Violence Says US Study, as Medical-Use Laws See Crime Fall." *Guardian*, January 13, 2018.
Dubin A. E., and A. Patapoutian. "Nociceptors: The Sensors of the Pain Pathway." *Journal of Clinical Investigation* 120, no. 11 (November 2010): 3760–72. https://www.jci.org/articles/view/42843.
Du Plessis, S. S., A. Agarwal, and A. Syriac. "Marijuana, Phytocannabinoids, the Endocannabinoid System, and Male Fertility." *Journal of Assisted Reproduction and Genetics* 32, no. 11 (2015):

1575–88.
Durst, R., H. Danenberg, R. Gallily, et al. “Cannabidiol, a Nonpsychoactive *Cannabis* Constituent, Protects against Myocardial Ischemic Reperfusion Injury.” *American Journal of Physiology: Heart and Circulatory Physiology* 293, no. 6 (December 2007): H3602–7.
Ebert, J. “Republicans Introduce Bill to Allow Medical Marijuana in Tennessee.” *Tennessean*, January 18, 2018. https://www.tennessean.com/story/news/politics/2018/01/18/republicans-introduce-bill-expand-medical-marijuana-tennessee/1044287001.
Elliott, S. “Mexico Just Legalized Medical Marijuana: But There’s a Catch,” *Herb*, June 19, 2017. https://herb.co/marijuana/news/mexico-legalized-medical-marijuana.
ElSohly, M. A., and D. Slade. “Chemical Constituents of Marijuana: The Complex Mixture of Natural Cannabinoids.” *Life Sciences* 78, no. 5 (2005): 539–48.
European Monitoring Centre for Drugs and Drug Addiction. “Austria: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/austria/drug-laws-and-offences_en.
———. “Belgium: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/belgium/drug-laws-and-offences_en.
———. “Czech Republic: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/czech-republic/drug-laws-and-offences_en.
———. “Greece: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/greece_en.
———. “Latvia: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/latvia/drug-laws-and-offences_en.
———. “Lithuania: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/lithuania/drug-laws-and-offences_en.
———. “Luxembourg: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/luxembourg/drug-laws-and-offences_en.
———. “Malta: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/malta/drug-laws-and-offences_en.
———. “Moldova: Country Overview.” http://www.emcdda.europa.eu/countries/moldova_en#laws.
———. “Portugal: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/portugal/drug-laws-and-offences_en.
———. “Slovenia: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/slovenia/drug-laws-and-offences_en.
———. “Spain: Country Drug Report 2017.” http://www.emcdda.europa.eu/countries/drug-reports/2017/spain/drug-laws-and-offences_en.
Evidence-Based Medicine Consult. “Substrates—Cytochrome P450 (Cyp) Enzymes Drug Table.” https://www.ebmconsult.com/content/pages/cytochrome-cyp-p450-enzyme-medication-herbs-substrates.
Feng, Y., F. Chen, and Q. Xia. “Pharmacologic Effects of Cannabidiol on Acute Reperfused Myocardial Infarction in Rabbits: Evaluated 3.0T Cardiac Magnetic Resonance Imaging and Histopathology.” *Journal of Cardiovascular Pharmacology* 66, no. 4 (October 2015): 354–63.
Fernández-Ruiz, J., M. A. Moro, and J. Martínez-Orgado. “Cannabinoids in Neurodegenerative Disorders and Stroke/Brain Trauma: From Preclinical Models to Clinical Applications.” *Neurotherapeutics* 12, no. 4 (2015): 793–806. doi:0.1007/s13311-015-0381-7.
Filbey, F. M., S. Aslan, V. D. Calhoun, et al. “Long-Term Effects of Marijuana Use on the Brain.” *Proceedings of the National Academy of Sciences of the United States of America* 111, no. 47 (November 2014): 16913–18. doi:10.1073/pnas.1415297111.
Földy, C., R. C. Malenka, and T. C. Südhof. “Autism-Associated Neuroligin-3 Mutations Commonly Disrupt Tonic Endocannabinoid Signaling.” *Neuron* 78, no. 3 (May 2013): 498–509. doi:10.1016/j.neuron.2013.02.036.

Ford, B. M., S. Tai, W. E. Fantegrossi, and P. L. Prather, “Synthetic Pot: Not Your Grandfather’s Marijuana.” *Trends in Pharmacological Sciences* 38, no. 3 (March 2017): 257–76. doi:10.1016/j.tips.2016.12.003.

“France to Issue On-the-Spot Fines for Cannabis Use.” *France 24*, January 25, 2018. http://www.france24.com/en/20180125-france-cannabis-drugs-spot-fines-collomb-macron.

Ganon-Elazar, E., and I. Akirav. “Cannabinoids Prevent the Development of Behavioral and Endocrine Alterations in a Rat Model of Intense Stress.” *Neuropsychopharmacology* 37 (August 2011). doi:10.1038/npp.2011.204.

Gavrilova, E., T. Kamada, and F. Zoutman. “Is Legal Pot Crippling Mexican Drug Trafficking Organisations? The Effect of Medical Marijuana Laws on US Crime.” *Economic Journal* (November 16, 2017). doi:10.1111/ecoj.12521.

Georgia General Assembly, SB 16, 2017–2018, http://www.legis.ga.gov/Legislation/en-US/display/20172018/SB/16.

Gertsch, J., M. Leonti, S. Raduner, et al. “Beta-Caryophyllene Is a Dietary Cannabinoid.” *Proceedings of the National Academy of Sciences of the United States of America* 105, no. 26 (July 1, 2008): 9099–9104. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2449371.

Giacoppo, S., G. Mandolino, M. Galuppo, P. Bramanti, and E. Mazzon. “Cannabinoids: New Promising Agents in the Treatment of Neurological Diseases.” *Molecules* 19, no. 11 (November 2014): 18781–816.

Gilman, J. M., J. K. Kuster, S. Lee, et al. “Cannabis Use Is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users.” *Journal of Neuroscience* 34, no. 16 (April 2014): 5529–38. doi:10.1523/JNEUROSCI.4745-13.2014.

Gotfried, J., R. Kataria, and R. Schey. “Review: The Role of Cannabinoids on Esophageal Function—What We Know Thus Far.” *Cannabis and Cannabinoid Research* 2, no. 1 (October 2017): 252–58. doi:10.1089/can.2017.0031.

Graham, J., M. Barberio, and G. S. Wang. “Capsaicin Cream for Treatment of Cannabinoid Hyperemesis Syndrome in Adolescents: A Case Series.” *Pediatrics* 140, no. 6 (November 2017): e20163795. doi:10.1542/peds.2016-3795.

Greer, G. R., C. S. Grob, and A. L. Halberstadt. “PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program.” *Journal of Psychoactive Drugs* 46, no. 1 (January–March 2014): 73. doi:10.1080/02791072.2013.873843.

Grimaldi, C., and A. Capasso. “Role of Lipid Rafts/Caveolae in the Anticancer Effect of Endocannabinoids.” *Mini-Reviews in Medicinal Chemistry* 12, no. 11 (2012): 1119–26.

Grinspoon, L., and J. B. Bakalar. “The Use of Cannabis as a Mood Stabilizer.” *Journal of Psychoactive Drugs* 30, no. 2 (April–June 1998): 171–77. doi:10.1080/02791072.1998.10399687.

Grotenhermen, F., and K. Müller-Vahl. “The Therapeutic Potential of Cannabis and Cannabinoids.” *Deutsches Ärzteblatt International* 109, nos. 29–30 (2012): 495–501. doi:10.3238/arztebl.2012.0495.

Gruden, G., F. Barutta, G. Kunos, and P. Pacher. “Role of the Endocannabinoid System in Diabetes and Diabetic Complications.” *British Journal of Pharmacology* 173, no. 7 (2016): 1116–27.

Guo, E. “Staunchly Anti-Pot Idaho Introduces Legislation to Allow CBD Oil.” *Inverse Culture*. January 26, 2018. https://www.inverse.com/article/40578-idaho-legislation-cbd-oil.

Gurney, J., C. Shaw, J. Stanley, V. Signal, and D. Sarfati. “Cannabis Exposure and Risk of Testicular Cancer: A Systematic Review and Meta-Analysis.” *BMC Cancer* 15 (2015): 897. https://doi.org/10.1186/s12885-015-1905-6.

Guzman, M. “Cannabinoids: Potential Anticancer Agents.” *Nature Reviews Cancer* 3, no. 10 (October 2003): 745–55. doi:10.1038/nrc1188.

H. Amdt. 748 to H.R. 4660. 113th Cong. (2013–2014). https://www.congress.gov/amendment/113th-congress/house-amendment/748.

Hampson, A. J. M. Grimaldi, J. Axelrod, and D. Wink. “Cannabidiol and (-) Delta9-Tetrahydrocannabinol Are Neuroprotective Antioxidants.” *Proceedings of the National Academy*

of Sciences of the United States of America 95, no. 14 (1998): 8268–73.
Harrison, P., "In New York," *Shamokin News-Dispath*, (March 1934).
Hartman, R. L., and M. Huestis. "Cannabis Effects on Driving Skills." *Clinical Chemistry* 59, no. 3 (February 2013): 478–92. doi:10.1373/clinchem.2012.194381.
Hayakawa, K., K. Mishima, and M. Fujiwara. "Therapeutic Potential of Non-Psychotropic Cannabidiol in Ischemic Stroke." *Pharmaceuticals* 3, no. 7 (2010): 2197–2212.
Hedegaard, H., M. Warner, and A. M. Miniño. "Drug Overdose Deaths in the United States, 1999–2016." NCHS Data Brief 294. December 2017. https://www.cdc.gov/nchs/products/databriefs/db294.htm.
Heishman, S. J., M. A. Huestis, J. E. Henningfield, and E. J. Cone, "Acute and Residual Effects of Marijuana: Profiles of Plasma THC Levels, Physiological, Subjective, and Performance Measures." *Pharmacology Biochemistry and Behav*ior 37, no. 3 (November 1990): 561–65. https://www.ncbi.nlm.nih.gov/pubmed/1965045.
Hill, K. P., M. D. Palastro, B. Johnson, and J. W. Ditre. "Cannabis and Pain: A Clinical Review." *Cannabis and Cannabinoid Research* 2, no. 1 (May 2017): 96–104. doi:10.1089/can.2017.0017.
Hill, M. N., and J. G. Tasker. "Endocannabinoid Signaling, Glucocorticoid-Mediated Negative Feedback, and Regulation of the Hypothalamic-Pituitary-Adrenal Axis." *Neuroscience* 204 (March 1, 2012): 5–16.
Hiltz, J. "1,600 New Reasons to Celebrate Medical Marijuana in Italy." *Marijuana.com*. September 26, 2016. https://www.marijuana.com/news/2016/09/1600-new-reasons-to-celebrate-medical-marijuana-in-italy.
———. "Greece Legalizes Medical Marijuana." *Marijuana.com*. July 5, 2017. https://www.marijuana.com/news/2017/07/greece-legalizes-medical-marijuana.
———. "Poland Legalizes Medical Marijuana." *Marijuana.com*. July 21, 2017. https://www.marijuana.com/news/2017/07/poland-legalizes-medical-marijuana.
Holland, J. "Daugaard: Yes on Teacher Pay, Yes on Medicaid Expansion, No on Medical Marijuana." *Rapid City Journal*, January 11, 2016. http://rapidcityjournal.com/news/local/gov-daugaard-yes-on-teacher-pay-yes-on-medicaid-expansion/article_640effab-2379-58b5-b078-124c4d5c6fe9.html.
Hollister, L. E. "Interactions of Cannabis with Other Drugs in Man." *NIDA Research Monograph* 68 (1986): 110–16.
Horváth, B., P. Mukhopadhyay, M. Kechrid, et al. "β-Caryophyllene Ameliorates Cisplatin-Induced Nephrotoxicity in a Cannabinoid 2 Receptor-Dependent Manner." *Free Radical Biology and Medicine* 52, no. 8 (2012): 1325–33. doi:10.1016/j.freeradbiomed.2012.01.014.
Hughes, A., R. N. Lipar, and M. Williams, "State Estimates of Adolescent Marijuana Use and Perceptions of Risk of Harm from Marijuana Use: 2013 and 2014," *CBHSQ Report*, December 17, 2015, https://www.samhsa.gov/data/sites/default/files/report_2121/ShortReport-2121.html.
Igimi, H., T. Hisatsugu, and M. Nishimura. "The Use of *D*-Limonene Preparation as a Dissolving Agent of Gallstones." *American Journal of Digestive Diseases* 21, no. 11 (November 1976): 926–39. https://doi.org/10.1007/BF01071903.
Illinois Department of Public Health. "Debilitating Conditions." November 1, 2016. http://www.dph.illinois.gov/topics-services/prevention-wellness/medical-cannabis/debilitating-conditions.
Indiana General Assembly, House Bill 1148, 2017, https://iga.in.gov/legislative/2017/bills/house/1148#document-f1053500.
———. "Medical Cannabis Patient Registry Program." http://www.dph.illinois.gov/topics-services/prevention-wellness/medical-cannabis.
Indiana General Assembly, House Bill 1148, 2017, https://iga.in.gov/legislative/2017/bills/house/1148#document-f1053500.
Industrial Hemp Farming Act of 2017. H.R. 3530, 115th Cong. (2017).
Ingraham, C. "Portugal Decriminalised Drugs 14 Years Ago—and Now Hardly Anyone Dies from

Overdosing." *Independent*, June 6, 2015. http://www.independent.co.uk/news/world/europe/portugal-decriminalised-drugs-14-years-ago-and-now-hardly-anyone-dies-from-overdosing-10301780.html.
Institute for Cannabis Therapeutics. "Additional Notes: Rescheduling of Cannabis." March 27, 2010. http://www.oregon.gov/pharmacy/imports/marijuana/staffreview/reschedulingcannabis-notes_3-10.pdf.
Insurance Institute for Highway Safety. *Status Report* 52, no. 4 (June 22, 2017).
Iowa Legislature, House File 524, 2017, https://www.legis.iowa.gov/legislation/BillBook?ga=87&ba=hf524.
Iversen, L. L. *The Science of Marijuana*. New York: Oxford University Press, 2008.
Izzo, A. A., F. Capasso, A. Costagliola, et al. "An Endogenous Cannabinoid Tone Attenuates Cholera Toxin-Induced Fluid Accumulation in Mice." *Gastroenterology* 125, no. 3 (September 2003): 765–74. https://www.ncbi.nlm.nih.gov/pubmed/12949722.
Izzo, A. A., N. Mascolo, and F. Capasso. "The Gastrointestinal Pharmacology of Cannabinoids." *Current Opinion in Pharmacology* 1, no. 6 (December 2001): 597–603. https://doi.org/10.1016/S1471-4892(01)00102-3.
Jetly, R., A. Heber, G. Fraser, and D. Boisvert. "The Efficacy of Nabilone, a Synthetic Cannabinoid, in the Treatment of PTSD-Associated Nightmares: A Preliminary Randomized, Double-Blind, Placebo-Controlled Cross-Over Design Study." *Psychoneuroendocrinology* 51 (January 2015): 585–88. doi:10.1016/j.psyneuen.2014.11.002.
Jiang, R., S. Yamaori, S. Takeda, I. Yamamoto, and K. Watanabe. "Identification of Cytochrome P4540 Enzymes Responsible for Metabolism of Cannabidiol by Human Liver Microsomes." *Life Sci*ences 89, nos. 5–6 (August 2011): 165–70. doi:10.1016/j.lfs.2011.05.018.
Joshi, M., A. Joshi, and T. Bartter. "Marijuana and Lung Diseases." *Current Opinion in Pulmonary Medicine* 20, no. 2 (March 2014): 173–79.
Jung, K. M., M. Sepers, C. M. Henstridge, et al. "Uncoupling of the Endocannabinoid Signalling Complex in a Mouse Model of Fragile X Syndrome." *Nature Communications* 3 (2012): 1080. doi:10.1038/ncomms2045.
Karniol, I. G., and E. A. Carlini. "Pharmacological Interaction between Cannabidiol and δ9-Tetrahydrocannabinol." *Psychopharmacologia* 3, no. 1 (1973): 53–70. https://doi.org/10.1007/BF00428793.
Karniol, I. G., I. Shirakawa, R. N. Takahashi, E. Knobel, and R. E. Musty. "Effects of Delta9-Tetrahydrocannabinol and Cannabinol in Man." *Pharmacology* 13, no. 6 (1975): 502–12. https://www.ncbi.nlm.nih.gov/pubmed/1221432.
Kirmizibekmez, H., I. Atay, M. Kaiser, et al. "Antiprotozoal Activity of *Melampyrum arvense* and Its Metabolites." *Phytotherapy Research* 25, no. 1 (July 7, 2010): 142–46. doi:10.1002/ptr.3233.
Komori, T., R. Fujiwara, M. Tanida, et al. "Effects of Citrus Fragrance on Immune Function and Depressive States." *Neuroimmunomodulation* 2 (1995): 174–80.
Koppel, B. S. "Cannabis in the Treatment of Dystonia, Dyskinesias, and Tics." *Neurotherapeutics* 12, no. 4 (2015): 788–92. doi:10.1007/s13311-015-0376-4.
Koppel, J., and P. Davies. "Targeting the Endocannabinoid System in Alzheimer's Disease." *Journal of Alzheimer's Disease* 15, no. 3 (2008): 495–504. doi:10.3233/JAD-2008-15315.
Kurz, R., and K. Blaas. "Use of Dronabinol (Delta-9-THC) in Autism: A Prospective Single-Case-Study with an Early Infantile Autistic Child." *Cannabinoids* 5, no. 4 (2010): 4–6.
Lacson, J. C. A., J. D. Carroll, E. Tuazon, E. J. Castelao, L. Bernstein, and V. K. Cortessis. "Population-Based Case-Control Study of Recreational Drug Use and Testis Cancer Risk Confirms Association between Marijuana Use and Non-Seminoma Risk." *Cancer* 118, no. 21 (2012): 5374–83.
Ladin, D. A., E. Soliman, L. Griffin, and R. Van Dross. "Preclinical and Clinical Assessment of Cannabinoids as Anti-Cancer Agents." *Frontiers in Pharmacology* 7 (2016): 361.
Lastres-Becker, I., F. Berrendero, J. J. Lucas, et al. "Loss of mRNA Levels, Binding and Activation

of GTP-Binding Proteins for Cannabinoid CB1 Receptors in the Basal Ganglia of a Transgenic Model of Huntington's Disease." *Brain Research Journal* 929, no. 2 (March 2002): 236–42.

Lastres-Becker, I., and J. Fernandez-Ruiz. "An Overview of Parkinson's Disease and the Cannabinoid System and Possible Benefits of Cannabinoid-Based Treatments." *Current Medicinal Chemistry* 13, no. 30 (2006): 3705–18.

Lastres-Becker, I., H. H. Hansen, F. Berrendero, et al. "Alleviation of Motor Hyperactivity and Neurochemical Deficits by Endocannabinoid Uptake Inhibition in a Rat Model of Huntington's Disease." *Synapse* 44, no. 1 (April 2002): 23–35.

Lee, M., S. M. Silverman, H. Hansen, V. B. Patel, and L. Manchikanti. "A Comprehensive Review of Opioid-Induced Hyperalgesia." *Pain Physician* 14 (2011): 145–61.

Lewis, S. E. M., C. Rapino, M. Di Tommaso, et al. "Differences in the Endocannabinoid System of Sperm from Fertile and Infertile Men." *PLoS One* 7, no. 10 (2012): e47704. https://doi.org/10.1371/journal.pone.0047704.

Li, H. L. "An Archaeological and Historical Account of Cannabis in China." *Economic Botany* 28, no. 4 (1973): 437–48.

LibertyPen. "Dr. Sanjay Gupta—Marijuana and Charlotte's Web." *YouTube. November 1, 2013.*https://www.youtube.com/watch?v=CiShwotFJR8.

Liesowska, A. "Iconic 2,500-Year-Old Siberian Princess 'Died from Breast Cancer,' Reveals MRI Scan." *Siberian Times*, October 14, 2014.

Ligresti, A., A. S. Moriello, K. Starowicz, et al. "Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma." *Journal of Pharmacology and Experimental Therapeutics* 318, no. 3 (September 2006): 1375–87.

Lin, Y., R. Shi, X. Wang, and H. M. Shen. "Luteolin, a Flavonoid with Potential for Cancer Prevention and Therapy." *Current Cancer Drug Targets* 8, no. 7 (November 2008): 634–46.

Lindsey, N. "Croatia's Groundbreaking Medical Cannabis Laws Make Global Impact." *Green Rush Daily*. June 24, 2016. https://greenrushdaily.com/croatia-makes-medical-marijuana-history.

Linge, R., L. Jiménez-Sánchez, L. Campa, et al. "Cannabidiol Induces Rapid-Acting Antidepressant-Like Effects and Enhances Cortical 5-HT/Glutamate Neurotransmission: Role of 5-HT1A Receptors." *Neuropharmacology* 103 (2016): 16–26.

Lisdahl, K. M., N. E. Wright, C. Kirchner-Medina, K. E. Maple, and S. Shollenbarger. "Considering Cannabis: The Effects of Regular Cannabis Use on Neurocognition in Adolescents and Young Adults." C*urrent Addiction Reports* 1 (2014): 144–56.

London, D. "Germany Legalizes Cannabis Prescriptions." *Marijuana.com*. January 19, 2017. https://www.marijuana.com/news/2017/01/germany-legalizes-cannabis-prescriptions.

———. "Luxembourg Prime Minister Promises Medical Marijuana." *Marijuana.com*. October 30, 2017. http://www.emcdda.europa.eu/countries/drug-reports/2017/latvia/drug-laws-and-offences_enhttps://www.marijuana.com/news/2017/10/luxembourg-prime-minister-promises-medical-marijuana.

López-Sendón, M. J. L., G. Caldentey, T. Cubillo, et al. "A Double-Blind, Randomized, Cross-Over, Placebo-Controlled, Pilot Trial with Sativex in Huntington's Disease." *Journal of Neurology* 263, no. 7 (2016): 1390–1400.

Louisiana State Legislature, Senate Bill No. 271, 2016, http://www.legis.la.gov/legis/ViewDocument.aspx?d=1003807.

Lozano, A. "Pesticides in Marijuana Growing Pose a Growing Problem for Cannabis Consumers." *Los Angeles Weekly*, October 27, 2016.

Lucas, P. "Cannabis as an Adjunct to or Substitute for Opiates in the Treatment of Chronic Pain." *Journal of Psychoactive Drugs* 44, no. 2 (April–June 2012): 125–33.

Lukhele, S. T., and L. R. Motadi. "Cannabidiol Rather than *Cannabis sativa* Extracts Inhibit Cell Growth and Induce Apoptosis in Cervical Cancer Cells." *BMC Complementary and Alternative Medicine* 16, no. 1 (2016): 335.

Maccarrone, M., H. Valensise, M. Bari, N. Lazzarin, C. Romanini, and A. Finazzi-Agrò. "Relation

between Decreased Anandamide Hydrolase Concentrations in Human Lymphocytes and Miscarriage." *Lancet* 355, no. 9212 (2000): 1326–29.
Maida, V., and P. J. Daeninck. "A User's Guide to Cannabinoid Therapies in Oncology." *Current Oncology* 23, no. 6 (2016): 398–406.
Manrique-Garcia, E., S. Zammit, C. Dalman, T. Hemmingsson, and P. Allebeck. "Cannabis Use and Depression: A Longitudinal Study of a National Cohort of Swedish Conscripts." *BMC Psychiatry* 12, no. 112 (2012). doi:10.1186/1471-244x-12-112.
"Marihuana Makes Fiends of Boys in 30 Days: Hasheesh Goads Users to Blood-Lust." *San Francisco Examiner*, January 31, 1923. http://www.druglibrary.org/mags/examiner23.htm.
Marijuana Doctors. "Medical Marijuana in Finland." 2018. https://www.marijuanadoctors.com/international-patients/finland.
———. "Updates to Medical Marijuana Program in Israel." October 4, 2017. https://www.marijuanadoctors.com/blog/israel-medical-marijuana-program-updates.
Marijuana Justice Act of 2017. S. 1689, 115th Cong. (2017).
McDonald, D. "The Racist Roots of Marijuana Prohibition." *Foundation for Economic Education*. April 11, 2017. https://fee.org/articles/the-racist-roots-of-marijuana-prohibition/.
McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, et al. "Cannabis and Schizophrenia." *Cochrane Database of Systematic Reviews*, no. 10 (2014): Art. No. CD004837.
McPartland, J., G. Guy, and V. DiMarzo, "Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions That Upregulate the Endocannabinoid System," edited by A. A. Romanovsky, *PLoS ONE* 9, no. 3 (2014): e89566, doi:10.1371/journal.pone.0089566.
McPartland, J. M. "The Endocannabinoid System: An Osteopathic Perspective." *Journal of the American Osteopathic Association* 108, no. 10 (October 2008): 586–600. doi:10.7556/jaoa.2008.108.10.586.
McPartland, J. M., I. Matias, V. Di Marzo, and M. Glass. "Evolutionary Origins of the Endocannabinoid System." *Gene* 370 (2006): 64–74. doi:10.1016/j.gene.2005.11.004.
Mechoulam, R. "Welcome and Keynote Speaker." CannMed Presentation, Boston, March 2016.
Mechoulam, R., and S. Ben-Shabat. "From Gan-Zi-Gun-Nu to Anandamide and 2-Arachidonoylglycerol: The Ongoing Story of Cannabis." *Natural Product Reports* 16 (1999): 131–43.
MedicalMarijuana.eu. "Guide to Cannabis for Chronic Pain Patients in Europe, 2016 Edition." 2016. http://irka.org.rs/wp-content/uploads/2014/09/Guide-to-Cannabis-for-Chronic-Pain-Patients-in-Europe.pdf.
Medical Marijuana Research Act of 2017. H.R. 3391, 115th Cong. (2017).
Meiri, D. "Matching an Effective Cannabis Strain Extract for a Specific Subtype of Cancer." CannMed Presentation, 2017.
Milekic, S. "Croatia Legalises Marijuana for Medical Use." *Balkan Insight*. October 15, 2015. http://www.balkaninsight.com/en/article/croatia-first-balkan-county-to-legalize-medical-marijuana-10-15-2015-1.
Ministry of Justice, Government of Jamaica. "Fact Sheet Prepared by the Ministry of Justice on the Dangerous Drugs (Amendment) Act of 2015." http://moj.gov.jm/news/dangerous-drugs-amendment-act-2015-fact-sheet.
Minnesota Department of Health, Office of Medical Cannabis, "Medical Cannabis and Intractable Pain," December 2, 2015, http://www.health.state.mn.us/topics/cannabis/intractable/intractablepainfs.pdf.
Mississippi Code §41-29-139, 2014, https://law.justia.com/codes/mississippi/2014/title-41/chapter-29/article-3/section-41-29-139.
Mississippi Legislature, House Bill 1231, 2014, http://billstatus.ls.state.ms.us/documents/2014/html/HB/1200-1299/HB1231SG.htm.
Mokrysz, C., R. Landy, S. H. Gage, M. R. Munafò, J. P. Roiser, and H. V. Curran. "Are IQ and

Educational Outcomes in Teenagers Related to Their Cannabis Use? A Prospective Cohort Study." *Journal of Psychopharmacology* 30, no. 2 (2016): 159–68. doi:10.1177/0269881115622241.

Morena, M., S. Patel, J. S. Bains, and M. N. Hill. "Neurobiological Interactions between Stress and the Endocannabinoid System." *Neuropsychopharmacology* 41, no. 1 (2015): 80–102. doi:10.1038/npp.2015.166.

Müller-Vahl, K. R., H. Kolbe, U. Schneider, and H. M. Emrich. "Cannabinoids: Possible Role in Patho-Physiology and Therapy of Gilles de la Tourette Syndrome." *Acta Psychiatrica Scandinavica* 98, no. 6 (1998): 502–6. doi:10.1111/j.1600-0447.1998.tb10127.x.

Naftali, T., L. Bar-Lev Schleider, I. Dotan, E. P. Lansky, F. Sklerovsky Benjaminov, and F. M. Konikoff. "Cannabis Induces a Clinical Response in Patients with Crohn's Disease: A Prospective Placebo-Controlled Study." *Clinical Gastroenterology and Hepatology* 11, no. 10 (2013): 1276–80.

National Center for Injury Prevention and Control. "Annual Surveillance Report of Drug-Related Risks and Outcomes." 2017.

New Jersey Compassionate Use Medical Marijuana Act, 2010, ftp://www.njleg.state.nj.us/20082009/S0500/119_R3.htm.

New York Mayor's Committee on Marihuana and the New York Academy of Medicine. "The Marihuana Problem in the City of New York." 1944.

Nguyen, B. M., D. Kim, S. Bricker, et al. "Effect of Marijuana Use on Outcomes in Traumatic Brain Injury." *American Surgeon* 80, no. 10 (October 2014): 979–83.

Nixon, R. "Remarks on Signing the Comprehensive Drug Abuse and Control Act of 1970." *American Presidency Project*. October 27, 1970. http://www.presidency.ucsb.edu/ws/?pid=2767.

North Carolina General Assembly, House Bill 1220/SL 2014-53, 2013–2014, https://www.ncleg.net/gascripts/BillLookUp/BillLookUp.pl?Session=2013&BillID=HB1220.

North Carolina General Assembly, House Bill 766/SL 2015-154, 2015–2016, https://www.ncleg.net/gascripts/BillLookUp/BillLookUp.pl?Session=2015&BillID=HB+766.

Nöthlings, U., S. P. Murphy, L. R. Wilkens, B. E. Henderson, and L. N. Kolonel. "Flavonols and Pancreatic Cancer Risk: The Multiethnic Cohort Study." *American Journal of Epidemiology* 166, no. 8 (October 2007): 924–31. https://doi.org/10.1093/aje/kwm172.

Office of Governor Larry Hogan. "Hogan-Rutherford Administration Declares State of Emergency, Announces Major Funding to Combat Heroin and Opioid Crisis in Maryland." Press Release, March 1, 2017. http://governor.maryland.gov/2017/03/01/hogan-rutherford-administration-declares-state-of-emergency-announces-major-funding-to-combat-heroin-and-opioid-crisis-in-maryland.

Office of the Secretary, US Department of Agriculture; Drug Enforcement Administration, Department of Justice; and Food and Drug Administration, Health and Human Services. "Statement of Principles on Industrial Hemp: A Notice by the Agriculture Department, the Drug Enforcement Administration, and the Food and Drug Administration." *Federal Register* (August 12, 2016). https://nifa.usda.gov/industrial-hemp.

Oláh, A., B. I. Tóth, I. Borbíró, et al. "Cannabidiol Exerts Sebostatic and Antiinflammatory Effects on Human Sebocytes." *Journal of Clinical Investigation* 124, no. 9 (2014): 3713–24.

O'Shaughnessy, W. B. "On Preparations of the Indian Hemp, or Gunjah." *Provencial Medical Journal* (February 1843).

Pacher, P., S. Bátkai, and G. Kunos. "The Endocannabinoid System as an Emerging Target of Pharmacotherapy." *Pharmacological Reviews* 58, no. 3 (2006): 389–462.

Pachico, E. "Why Did Ecuador Toughen Up Drug Laws?" *InSight Crime*. October 3, 2015. https://www.insightcrime.org/news/brief/why-did-ecuador-toughen-up-drug-laws.

Palliyaguru, D. L., and F. Wu. "The Global Geographical Overlap of Aflatoxin and Hepatitis C: Controlling Risk factors for Liver Cancer Worldwide." *Food Additives and Contaminants, Part A: Chemistry, Analysis, Control, Exposure and Risk Assessment* 30, no. 3 (2013): 534–40.

Pazos, M. R., N. Mohammed, H. Lafuente, et al. “Mechanisms of Cannabidiol Neuroprotection in Hypoxic-Ischemic Newborn Pigs: Role of 5HT(1)A and CB2 Receptors.” *Neuropharmacology* 71 (2013): 282–91.

Penner, E. A., H. Buettner, and M. A. Mittleman. “The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults.” *American Journal of Medicine* 126, no. 7 (July 2013): 583–89. doi:10.1016/j.amjmed.2013.03.002.

Perkins, J. M. and S. N. Davis, “Endocannabinoid System Overactivity and the Metabolic Syndrome: Prospects for Treatment,” *Current Diabetes Reports* 8, no.1 (February 2008): 12–19.

Pertwee, R. G. “Cannabinoid Receptors and Pain.” *Progress in Neurobiology* 63 (2001): 569–611.

———. “The Diverse CB1 and CB2 Receptor Pharmacology of Three Plant Cannabinoids: D9-Tetrahydrocannabinol, Cannabidiol and D9-Tetrahydrocannabivarin.” *British Journal of Pharmacology* 153, no. 2 (2008): 199–215.

Piomelli, D. “The Molecular Logic of Endocannabinoid Signaling.” *Nature Reviews Neuroscience* 4 (2003): 873–84.

Piomelli, D., and E. B. Russo. “The *Cannabis sativa* versus *Cannabis indica* Debate: An Interview with Ethan Russo, MD.” *Cannabis and Cannabinoid Research* 1, no. 1 (2016): 44–46.

Plasse, T. F., R. W. Gorter, S. H. Krasnow, M. Lane, K. V. Shepard, and R. G. Wadleigh. “Recent Clinical Experience with Dronabinol.” *Pharmacology Biochemistry and Behavior* 40, no. 3 (November 1991): 701–8.

Polosmak, N., and C. O’Rear. “A Mummy Unearthed from the Pastures of Heaven.” *National Geographic* (October 1994): 80–103.

Priya S, L. “5 Most Interesting Private Member Bills of 2017.” *Better India*. January 4, 2018. https://www.thebetterindia.com/126700/5-private-member-bills-2017-passed-parliament.

PubChem. “Beta-Ocimene,” https://pubchem.ncbi.nlm.nih.gov/compound/_E_-beta-ocimene#section=Pharmacology-and-Biochemistry.

———. “Caryophyllene.” https://pubchem.ncbi.nlm.nih.gov/compound/5281515#section=Literature.

———. “D-Limonene.” https://pubchem.ncbi.nlm.nih.gov/compound/440917.

Quistad, C. B., S. E. Sparks, and J. E. Casida. “Fatty Acid Amide Hydrolase Inhibition by Neurotoxic Organophosphorus Pesticides.” *Toxicology and Applied Pharmacology* 173 (2001): 48–55.

Radhakrishnan, R., S. T. Wilkinson, and D. C. D’Souza. “Gone to Pot: A Review of the Association between Cannabis and Psychosis.” *Frontiers in Psychiatry* 5 (2014): 54.

Ramírez, B. G., C. Blázquez, T. Gómez del Pulgar, M. Guzmán, and M. L. de Ceballos. “Prevention of Alzheimer’s Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation.” *Journal of Neuroscience*, 25 no. 8 (February 23, 2005): 1904–13.

Ramsey, G. “Getting Regulation Right: Assessing Uruguay’s Historic Cannabis Initiative.” *Washington Office on Latin America*. November 2016. http://druglawreform.info/en/issues/cannabis/item/7254-getting-regulation-right.

Raschi, M. “Marijuana Coltivata a San Marino per Curare I Malati.” *Il Resto del Carlino*. July 18, 2016. http://www.ilrestodelcarlino.it/rimini/cronaca/cannabis-marijuana-san-marino-1.2357222.

Realm of Caring. “AED Potential Interactions with CBD.” https://theroc.us/images/aedinteractions.pdf.

Rebeiro, L. I., and P. W. Ind. “Effect of Cannabis Smoking on Lung Function and Respiratory Symptoms: A Structured Literature Review.” *NPJ: Primary Care Respiratory Medicine* 16071 (2016).

Redazione. “San Marino Legalizza la Cannabis Terapeutica (e intende anche produrla).” *Dolce Vita Online*. June 29, 2016. http://www.dolcevitaonline.it/san-marino-ha-legalizzato-la-cannabis-terapeutica-e-intende-anche-produrla.

Reinarman, C., H. Nunberg, F. Lanthier, and T. Heddleston. “Who Are Medical Marijuana

Patients? Population Characteristics from Nine California Assessment Clinics." *Journal of Psychoactive Drugs* 43, no. 2 (2011): 128–35.
Releaf App. https://releafapp.com/about-us.
Reuters Staff. "Chilean Pharmacies Begin Marijuana Medicine Sales in First for Latam." *Reuters*. May 10, 2017. https://www.reuters.com/article/us-chile-marijuana/chilean-pharmacies-begin-marijuana-medicine-sales-in-first-for-latam-idUSKBN1862OE.
———. "Peru Congress Passes Bill to Legalize Medical Marijuana." *Reuters*. October 20, 2017. https://www.reuters.com/article/us-peru-marijuana/peru-congress-passes-bill-to-legalize-medical-marijuana-idUSKBN1CP1JP.
Riedl, M. "City Gives Initial OK on Marijuana Ordinance." *Wichita Eagle*, June 7, 2017. http://www.kansas.com/news/politics-government/article154613664.html.
Rivas del Silva, A. C., P. M. Lopes, M. M. Barros de Azevedo, D. C. Costa, C. S. Alviano, and D. S. Alviano. "Biological Activities of α-Pinene and β-Pinene Enantiomers." *Molecules* 17, no. 6 (May 25, 2012): 6305–16. doi:10.3390/molecules17066305.
Rivat, C., C. Becker, A. Blugeot, et al. "Chronic Stress Induces Transient Spinal Neuroinflammation, Triggering Sensory Hypersensitivity and Long-Lasting Anxiety-Induced Hyperalgesia." *Journal of Pain* 150, no. 2 (August 2010): 358–68.
Robinson, K. J., S. D. Twiss, N. Hazon, and P. P. Pomeroy. "Maternal Oxytocin Is Linked to Close Mother-Infant Proximity in Grey Seals (*Halichoerus grypus*)." *PLoS One* 10, no. 12 (2015): e0144577.
Rock, E. M., and L. A. Parker. "Synergy between Cannabidiol, Cannabidiolic Acid, and Δ9-Tetrahydrocannabinol in the Regulation of Emesis in the *Suncus murinus* (House Musk Shrew)." *Behavioral Neuroscience* 129, no. 3 (2015): 368–70.
Rodríguez de Fonseca, F., I. Del Arco, F. J. Bermudez-Silva, A. Bilbao, A. Cippitelli, and M. Navarro. "The Endocannabinoid System: Physiology and Pharmacology." *Alcohol and Alcoholism* 40, no. 1 (2005): 2–14.
Rodríguez de Fonseca, F., I. Del Arco, J. L. Martin-Calderon, M. A. Gorriti, and M. Navarro. "Role of the Endogenous Cannabinoid System in the Regulation of Motor Activity." *Neurobiology of Disease* 5, no. 6 (1998): 483–501.
Rodríguez de Fonseca, F., M. Navarro, R. Gómez, et al. "An Anorexic Lipid Mediator Regulated by Feeding." *Nature* 414, no. 6860 (2001): 209–12.
Rogers, B. "Justin Trudeau Confirms That Canada's Marijuana Legalization Date Won't Actually Be July 1st, 2018." *Narcity*. 2018. https://www.narcity.com/news/justin-trudeau-confirms-that-canadas-marijuana-legalization-date-wont-actually-be-july-1st-2018.
Romano, B., F. Borrelli, E. Pagano, M. G. Cascio, R. G. Pertwee, and A. A. Izzo. "Inhibition of Colon Carcinogenesis by a Standardized *Cannabis sativa* Extract with High Content of Cannabidiol." *Phytomedicine* 21, no. 5 (April 15, 2014): 631–39. doi:10.1016/j.phymed.2013.11.006.
Ross, S. A., and M. A. ElSohly. "The Volatile Oil Composition of Fresh and Air-Dried Buds of *Cannabis sativa*." *Journal of Natural Products* 59, no. 1 (1996): 49–51.
Ruby, M. A., D. K. Nomura, C. S. Hudak, et al., "Overactive Endocannabinoid Signaling Impairs Apolipoprotein E-Mediated Clearance of Triglyceride-Rich Lipoproteins," *Proceedings of the National Academy of Sciences* 105, no. 38 (September 2008): 14561–66, doi:10.1073/pnas.0807232105.
Russo, E. "Taming THC: Potential Cannabis Synergy and Phytocannabinoid-Terpenoid Entourage Effects." *British Journal of Pharmacology* 163, no. 7 (August 2011): 1344–64. doi:10.1111/j.1476-5381.2011.01238.x.
Russo, E. B. "Clinical Endocannabinoid Deficiency (CECD): Can This Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and Other Treatment-Resistant Conditions?" *Neuroendocrinology Letters* 25, nos. 1–2 (2003): 31–39.
———. "Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the

Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes." *Cannabis and Cannabinoid Research* 1, no. 1 (2016): 154–65. doi:10.1089/can.2016.0009.

Russo, E. B., and G. W. Guy. "A Tale of Two Cannabinoids: The Therapeutic Rationale for Combining Tetrahydrocannabinol and Cannabidiol." *Medical Hypotheses* 66, no. 4 (2006): 234–46.

Ryberg, E., N. Larsson, S. Sjögren, et al. "The Orphan Receptor GPR55 Is a Novel Cannabinoid Receptor." *British Journal of Pharmacology* 152, no. 7 (2007): 1092–1101.

Sachs, J., E. McGlade, and D. Yurgelun-Todd. "Safety and Toxicology of Cannabinoids." *Neurotherapeutics* 12, no. 4 (2015): 735–46.

Sachse-Seeboth, C., J. Pfeil, D. Sehrt, et al. "Interindividual Variation in the Pharmacokinetics of Delta9-Tetrahydrocannabinol as Related to Genetic Polymorphisms in CYP2C9." *Clinical Pharmacology and Therapeutics* 85, no. 3 (March 2009): 273–76.

Sagredo O., M. R. Pazos, S. Valdeolivas, and J. Fernández-Ruiz. "Cannabinoids: Novel Medicines for the Treatment of Huntington's Disease." *Recent Patents on CNS Drug Discovery* 7, no. 1 (2012): 41–48.

Santiago, J. V. A., J. Jayachitra, M. Shenbagam, and N. Nalini. "Dietary D-Limonene Alleviates Insulin Resistance and Oxidative Stress-Induced Liver Injury in High-Fat Diet and L-NAME-Treated Rats." *European Journal of Nutrition* 51, no. 1 (February 2012): 57–68. doi:10.1007/s00394-011-0182-7.

Sarfaraz, S., V. M. Adhami, and D. N. Syed. "Cannabinoids for Cancer Treatment: Progress and Promise." *Cancer Research* 68, no. 2 (January 2008): 338–42.

Sarfaraz, S., F. Afaq, V. M. Adhami, A. Malik, and H. Mukhtar. "Cannabinoid Receptor Agonist-Induced Apoptosis of Human Prostate Cancer Cells LNCaP Proceeds through Sustained Activation of ERK1/2 Leading to G1 Cell Cycle Arrest." *Journal of Biological Chemistry* 281 (2006): 39480–91.

Schicho, R., and M. Storr. "Alternative Targets within the Endocannabinoid System for Future Treatment of Gastrointestinal Diseases." *Canadian Journal of Gastroenterology* 25, no. 7 (2011): 377–83.

Schröder, S., K. Beckmann, G. Franconi, et al. "Can Medical Herbs Stimulate Regeneration or Neuroprotection and Treat Neuropathic Pain in Chemotherapy-Induced Peripheral Neuropathy?" *Evidence-Based Complementary and Alternative Medicine* (2013): 423713.

Schurman, L. D., and A. H. Lichtman. "Endocannabinoids: A Promising Impact for Traumatic Brain Injury." *Frontiers in Pharmacology* 8 (2017): 69.

Schwarcz, G., and B. Karajgi. "Improvement in Refractory Psychosis with Dronabinol: Four Case Reports." *Journal of Clinical Psychiatry* 71, no. 11 (November 2011): 1552–53.

Schwarcz, G., B. Karajgi, and R. McCarthy. "Synthetic Delta-9-Tetrahydrocannabinol (Dronabinol) Can Improve the Symptoms of Schizophrenia." *Journal of Clinical Psychopharmacology* 29, no. 3 (June 2009): 255–58. doi:10.1097/JCP.0b013e3181a6bc3b.

Scott, J. C., S. T. Slomiak, J. D. Jones, et al., "Association of Cannabis with Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Metaanalysis," *JAMA Psychiatry* (April 2018), doi:10.1001/jamapsychiatry.2018.0335.

Sessions, J. B. "Marijuana Enforcement." January 4, 2018. https://www.justice.gov/opa/press-release/file/1022196/download.

Shelef, A., Y. Barak, U. Berger, et al. "Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An Open Label, Add-On, Pilot Study." *Journal of Alzheimer's Disease* 51, no. 1 (2016): 15–19.

Shinjyo, N., and V. Di Marzo. "The Effect of Cannabichromene on Adult Neural Stem/Progenitor Cells." *Neurochemistry International* 63, no. 5 (2013): 432–37. doi:10.1016/j.neuint.2013.08.002.

Shmist, Y. A., I. Goncharov, M. Eichler, et al. "Delta-9-Tetrahydrocannabinol Protects Cardiac Cells from Hypoxia via CB2 Receptor Activation and Nitric Oxide Production." *Molecular and Cellular Biochemistry* 283, nos. 1–2 (February 2006): 75–83.

Simopoulos, A. P. “The Importance of the Ratio of Omega-6/Omega-3 Essential Fatty Acids.” *Biomedicine and Pharmacotherapy* 56, no. 8 (October 2002): 365–79.
Single Convention on Narcotic Drugs. New York, March 30, 1961.
Small, E., “Evolution and Classification of *Cannabis sativa* (Marijuana, Hemp) in Relation to Human Utilization.” *Botanical Review* 81 (2015):189–294.
Smokers Club. “Turkey Legalized a Farm of Medical Marijuana.” March 1, 2016. http://www.thesmokersclub.com/news/international-news/turkey-legalized-a-form-of-medical-marijuana.
Snir, A., D. Nadel, I. Groman-Yaroslavski, et al. “The Origin of Cultivation and Proto-Weeds, Long before Neolithic Farming.” *PLOS One* 10, no. 7 (July 2015): e0131422. https://doi.org/10.1371/journal.pone.0131422.
South Carolina General Assembly, A221, R229, S1035, 2014, http://www.scstatehouse.gov/sess120_2013-2014/bills/1035.htm.
State of Connecticut, House Bill No. 5389, Public Act No. 12-55, 2012, https://www.cga.ct.gov/2012/ACT/PA/2012PA-00055-R00HB-05389-PA.htm.
State of Oklahoma, House Bill No. 2835, 2016, http://webserver1.lsb.state. ok.us/cf_pdf/2015-16%20ENR/hB/HB2835%20ENR.PDF.
Stella, N., P. Schweitzer, and D. Piomelli. “A Second Endogenous Cannabinoid That Modulates Long-Term Potentiation.” *Nature* 388 (1997): 773–78.
Stiles, J., and T. L. Jernigan. “The Basics of Brain Development.” *Neuropsychological Review* 20, no. 4 (December 2010): 327–48.
Stout, S. M., and N. M. Cimino. “Exogenous Cannabinoids as Substrates, Inhibitors, and Inducers of Human Drug Metabolizing Enzymes: A Systematic Review.” *Drug Metabolism Reviews* 46 (2014): 86–95.
Sugiura, T., S. Kondo, A. Sukagawa, et al. “2-Arachidonoylglycerol: A Possible Endogenous Cannabinoid Receptor Ligand in Brain.” *Biochemistry Biophysics Research Communications* 215 (1995): 89–97.
Sun, A. J., and M. L. Eisenberg. “Association between Marijuana Use and Sexual Frequency in the United States: A Population-Based Study.” *Journal of Sexual Medicine* 14, no. 11 (November 2017): 1342–47.
Surkin, P. N., S. L. Gallino, V. Luce, F. Correa, J. Fernandez-Solari, and A. De Laurentiis. “Pharmacological Augmentation of Endocannabinoid Signaling Reduces the Neuroendocrine Response to Stress.” *Psychoneuroendocrinology* 87 (January 2018): 131–40.
Takeda, S. “Cannabidiolic Acid-Mediated Selective Down-Regulation of C-Fos in Highly Aggressive Breast Cancer MDA-MB-231 Cells: Possible Involvement of Its Down-Regulation in the Abrogation of Aggressiveness.” *Journal of Natural Medicine* 71, no. 1 (January 2017): 286–91. doi:10.1007/s11418-016-1030-0.
Takeda, S., K. Misawa, I. Yamamoto, and K. Watanabe. “Cannabidiolic Acid as a Selective Cyclooxygenase-2 Inhibitory Component in Cannabis.” *Drug Metabolism and Disposition* 36, no. 9 (2008): 1917–21. http://doi.org/10.1124/dmd.108.020909.
Tart, C. T. “Marijuana Intoxication: Common Experiences.” *Nature* 226 (May 23, 1970): 701–4.
Tau, G. Z., and B. S. Peterson. “Normal Development of Brain Circuits.” *Neuropsychopharmacology Reviews* 35 (2010): 147–68.
Taupin, P. “Apigenin and Related Compounds Stimulate Adult Neurogenesis—Mars, Inc., the Salk Institute for Biological Studies.” *Expert Opinion on Therapeutic Patents* 19 (2009): 523–27.
Texas Department of Public Safety. “Compassionate Use Program.” https://www.dps.texas.gov/rsd/CUP/index.htm.
Therapeutic Hemp Medical Access Act of 2017. S. 1008, 115th Cong.” www.GovTrack.us. (2017).
Thompson, G. R., J. M. Tuscano, M. Dennis, et al. “A Microbiome Assessment of Medical Marijuana.” *Clinical Microbiology and Infection* 23, no. 4 (April 2017): 269–70. http://dx.doi.org/10.1016/j.cmi.2016.12.001.

Timberlake, D. S. “A Comparison of Drug Use and Dependence between Blunt Smokers and Other Cannabis Users.” *Substance Use and Misuse* 44, no. 3 (2009): 401–15. doi:10.1080/10826080802347651.

TNI Drugs and Democracy Programme. “Belize GG Assents to Legislation Allowing for Decriminalisation of Marijuana.” November 4, 2017. http://druglawreform.info/en/country-information/caribbean/belize.

———. “Brazil.” http://druglawreform.info/en/country-information/latin-america/brazil/item/201-brazil.

———. “Costa Rica.” http://druglawreform.info/en/country-information/central-america/costa-rica.

———. “Ecuador.” http://druglawreform.info/en/country-information/latin-america/ecuador.

———. “Mexico.” http://druglawreform.info/en/country-information/mexico/item/205-mexico.

———. “Paraguay: Decriminalization.” http://druglawreform.info/en/country-information/latin-america/paraguay/item/206-paraguay.

———. “Venezuela.” http://druglawreform.info/en/country-information/latin-america/venezuela.

Törmäkangas, L., P. Vuorela, E. Saario, M. Leinonen, P. Saikku, and H. Vuorela. “In Vivo Treatment of Acute *Chlamydia pneumoniae* Infection with the Flavonoids Quercetin and Luteolin and an Alkyl Gallate, Octyl Gallate, in a Mouse Model.” *Biochemical Pharmacology* 70 (November 2005): 1222–30. doi:10.1016/j.bcp.2005.07.012.

Trustees of Indiana University. “The Flockhart Table.” http://medicine.iupui.edu/clinpharm/ddis/main-table.

Turner, T. “Odds and Ends of Life in Los Angeles.” *Los Angeles Times*, August 11, 1935. F30.

Ungar, P. S. *Evolution’s Bite: A Story of Teeth, Diet, and Human Origins*. Princeton, NJ: Princeton University Press, 2017.

United States Commission on Marihuana and Drug Abuse. *Marihuana: A Signal of Misunderstanding*. Washington, DC: US Government Printing Office, 1972.

United States Patent Office. Patent no. 2,130,523. September 20, 1938. https://patentimages.storage.googleapis.com/19/04/3e/5792825895c30e/US2130523.pdf.

Upton R., L. Craker, M. ElSohly, A. Romm, E. Russo, and M. Sexton, eds. *Cannabis Inflorescence (*Cannabis *spp.): Standards of Identity, Analysis, and Quality Control*. Rev. Scotts Valley, CA: American Herbal Pharmacopoeia, 2014.

US Department of Justice, Drug Enforcement Administration. “Marijuana Rescheduling Petition, DEA Docket No. 86-22.” September 6, 1988.

Van Booven, D., S. Marsh, H. McLeod, et al. “Cytochrome P450 2C9-CYP2C9.” *Pharmacogenetics and Genomics* 20, no. 4 (2010): 277–81. doi:10.1097/FPC.0b013e3283349e84.

Van der Pol, P., N. Liebregts, R. de Graaf, et al. “Mental Health Differences between Frequent Cannabis Users with and without Dependence and the General Population.” *Addiction* 108, no. 8 (2013): 1459–69.

Vargas, D. L., C. Nascimbene, and C. Krishnan. “Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism.” *Annals of Neurology* 57, no. 1 (January 2005): 67–81.

Veterans Equal Access Act. H.R. 1820, 115th Cong. (2017), https://www.congress.gov/bill/115th-congress/house-bill/1820.

Volkow, N. D. “Marijuana’s Lasting Effects on the Brain.” *National Institute on Drug Abuse*. March 2013. https://www.drugabuse.gov/about-nida/directors-page/messages-director/2012/09/marijuanas-lasting-effects-brain.

Waldman, M., E. Hochhauser, M. Fishbein, D. Aravot, A. Shainberg, and Y. Sarne. “An Ultra-Low Dose of Tetrahydrocannabinol Provides Cardioprotection.” *Biochemical Pharmacology* 85, no. 11 (June 1, 2013): 1626–33. doi:10.1016/j.bcp.2013.03.014.

Walsh, S. K., C. Y. Hepburn, K. A. Kane, and C. L. Wainwright. “Acute Administration of Cannabidiol In Vivo Suppresses Ischaemia-induced Cardiac Arrhythmias and Reduces Infarct Size When Given at Reperfusion.” *British Journal of Pharmacology* 160, no. 5 (July 2010):

1234–42.
Ware, M. A., T. Wang, S. Shapiro, et al. “Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial.” *Canadian Medical Association Journal* 182, no. 14 (2010): E694–E701.
Watanabe, K., S. Yamaori, T. Funahashi, T. Kimura, and I. Yamamoto. “Cytochrome P450 Enzymes Involved in the Metabolism of Tetrahydrocannabinols and Cannabinol by Human Hepatic Microsomes.” *Life Sciences* 80, no. 15 (March 2007): 1415–19.
Web Guides. “Primary Documents in American History: 18th Amendment to the U.S. Constitution (Prohibition).” October 30, 2017. https://www.loc.gov/rr/program/bib/ourdocs/18thamendment.html.
Weiland, B. J., R. E. Thayer, B. E. Depue, A. Sabbineni, A. D. Bryan, and K. E. Hutchison. “Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults.” *Journal of Neuroscience* 35, no. 4 (January 28, 2015): 1505–12.
Wiech K, and I. Tracey. “The Influence of Negative Emotions on Pain: Behavioral Effects and Neural Mechanisms.” *NeuroImage* 47, no. 3 (September 2009): 987–94.
Wilms H, L. Zecca, P. Rosenstiel, J. Sievers, G. Deuschl, and R. Lucius. “Inflammation in Parkinson’s Diseases and Other Neurodegenerative Diseases: Cause and Therapeutic Implications.” *Current Pharmaceutical Design* 13, no. 18 (2007): 1925–28.
Wilsey, B., T. Marcotte, R. Deutsch, B. Gouaux, S. Sakai, and H. Donaghe. “Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain.” *Journal of Pain* 14, no. 2 (2013): 136–48.
World Health Organization, “WHO Recommends the Most Stringent Level of International Control for Synthetic Opioid Carfentanil,” December 13, 2017, http://www.who.int/medicines/news/2017/WHO-recommends-most-stringent-level-int-control/en.
Zalesky A, N. Solowij, M. Yücel, et al. “Effect of Long-Term Cannabis Use on Axonal Fibre Connectivity.” *Brain* 135, pt. 7 (July 2012): 2245–55. doi:10.1093/brain/aws136.
Zhang, J.-M., and J. An. “Cytokines, Inflammation and Pain.” *International Anesthesiology Clinics* 45, no. 2 (2007): 27–37.
Zuardi, A. W., J. A. Crippa, J. E. Hallak, et al. “Cannabidiol for the Treatment of Psychosis in Parkinson’s Disease.” *Journal of Psychopharmacology* 23, no. 8 (November 2009): 979–83.

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About the Author

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