A SURGEON'S PERSPECTIVE ON THE SCIENCE & TRUTH OF CANNABIS

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RESERVE:MD™

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INTRODUCTION

Nearly every individual I have met who is involved in the cannabis industry has a unique story to tell. Whether they are a farmer, scientist, healthcare provider, business owner, health enthusiast, or simply a recreational user, most have chosen to pursue this area despite the challenging political landscape. I continue to meet individuals extremely passionate about cannabis for one simple reason … they believe in its value. My education in medical cannabis has been slow and incremental. After graduating from medical school in 2004 from Loyola University Chicago, I spent six years as an intern, resident, and fellow at Brown University before becoming board certified in both general surgery and gastrointestinal surgery/colon and rectal surgery. Since entering private practice in 2010, I've treated tens of thousands of patients for nearly every disease affecting the gastrointestinal system including gastrointestinal cancers, inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, chronic abdominal pain, and gastroesophageal reflux disease, just to name a few.

In this time, the social, cultural, and political climate surrounding medical cannabis in the United States has changed a great deal. Although federal law still prohibits the possession or use of cannabis—even for medical purposes—under the Controlled Substances Act of 1970, popular support for overturning these restrictions has grown overwhelmingly in recent decades, thanks in part to the advocacy work of groups such as Americans for Safe Access. On the state level—in a process which began before I'd graduated college—the law has proven increasingly open to permitting doctors to prescribe cannabis to their patients, and well before these adjustments were extended to my home state of New York, my own patients would broach the topic of medical cannabis on a regular basis—usually while discussing treatment plans for Crohn's disease, ulcerative colitis, irritable bowel syndrome, or colon or rectal cancers.

Often, my patients had already made up their minds: they were convinced that cannabis could help them, and had begun using it. Many had planned to relocate to a state where the law had already changed, while others had made arrangements to access cannabis illegally. I was grateful for their honesty, but this "admission of guilt" presented me with a personal dilemma: Even if I didn't

object to what my patients were doing, how could I advise anyone on the efficacy of a drug I knew little about?

Before I could make any kind of ruling on whether cannabis could do more good than harm, I felt duty-bound to gather as much data on the topic as possible. Over the next five years, I pored over whatever reputable journals and textbooks I could find whose authors were taking cannabinoid therapy seriously. I read as much as I possibly could on the subject, and even traveled to Israel to visit the Hebrew University Multidisciplinary Center on Cannabinoid Research, in Jerusalem, meeting with Raphael Mechoulam, a Nobel Prize nominee, and one of the world's foremost investigators of the makeup and pharmacological potential of the cannabis plant. Things got somewhat easier for me in 2014, when cannabis was finally legalized in New York State for medical purposes, and I soon developed a network of referring providers who had affirmed their support for advising our patients to use cannabis in cases we deemed appropriate. As of this writing, I've recommended cannabis therapy for thousands of patients, as well as individuals wishing to enhance their health through the use of cannabis.

The outcomes, while anecdotal, have been enormously encouraging. Patients who were undergoing radiation chemotherapy had fewer bouts of nausea or decreased appetite. Others, who'd been experiencing pain or discomfort from surgery, found they needed less of their conventional pain medications, including opioids. As I expanded my practice beyond treatments for gastrointestinal ailments, I soon saw a number of patients with neurological conditions; they, too, reported reduced symptoms and dependence on conventional medication.

During the last five years, at least 90% of the people to whom I'd prescribed medical cannabis reported an improved overall quality of life. Interestingly, about 20% of these patients sought out products that did not contain tetrahydrocannabinol (THC), the principal psychoactive ingredient in cannabis. In other words, they wanted to find products that could address their symptoms, but they weren't interested in getting "high." Many of these people were put off by the stigma of cannabis, or were vexed by the possibility of failing a drug test. Others simply didn't like being impaired.

As more and more people have come to me with questions about cannabis, I've remained dedicated to patient safety, and to sharing information that is assiduously truthful and well-supported. In addition to my membership on the Society of Cannabis Clinicians and the American Academy of Cannabinoid Medicine, I now serve as chairman of the Dispensary Review Committee for the Association of Cannabis Specialists, whose main purpose is to ensure that dispensaries operate safely and responsibly, and uphold best practices when

educating their customers. In 2016, I founded a company, Reserve:MD™, to develop a line of products that would optimize the human body's interaction with the active ingredients in cannabis, and I continue to give presentations on medical cannabis around the country to fellow professionals and the general public at hospitals, hospices, libraries, clinics, and community centers.

I am passionate about this subject. As the legal and political landscape around cannabis continues to evolve, I want to do what I can to help people who are considering using it to treat disease and improve their quality of life, and I have made it a priority to share the fruits of my research and experience as a clinician with as large an audience as possible. In reading this book, I hope you'll benefit from what I've learned.

Section I

THE PROMISE OF CANNABIS

1

HISTORY

Medical cannabis is at once ultra-modern development, and a practice that goes back for millennia. It is impossible to say where or when the cannabis plant was first discovered, but most experts believe it first appeared around 36 million years ago in the Altai Mountains of Central Asia.[1] Traces of dried cannabis flower found in a clay jar at a Jõmon-era excavation site, in Japan, have been dated to around 7,000 BCE, while the oldest written reports of medical use emerged in China at approximately 2,800 BCE.[2]

At around this time, the Emperor Shen-Nung cited cannabis as an herb whose therapeutic potential was comparable to ginseng and ephedra. Later, in the second century BCE, the well-known Chinese surgeon Hua T'o is said to have performed complicated incisions and organ grafts, and to have anaesthetized his patients with a preparation of cannabis and wine known as *ma-yo*.[3] The plant was also cited as an effective source of oil, fiber, and intoxicating medicine in ancient Mesopotamia, and comes up in several Egyptian texts beginning in the early second millennium BCE, where it is suggested as part of a topical preparation for ingrown toe- and fingernails, and for inflammations of the vagina.[4] [5] The Hebrew Bible, in the Book of Exodus, mentions what is probably cannabis (*kaneh bosem*) in the description of the tabernacle and altar, among the list of requirements for ritual sacrifices and incense; in this context, the word *kan* is translated as "reed," and *bosem* is read to mean, "aromatic."[6] Several Roman physicians prescribed cannabis at the dawn of the common era, including Calen and Pliny the Elder, as well as Pedanius Dioscorides, a doctor who served the emperor Nero in the first century CE, and who recommended the herb for ailments such as earache.[7]

During the medieval period, cannabis continued to proliferate throughout the Mediterranean, the Middle East, and South Asia, but its use in the West faded rapidly. In 1484, Pope Innocent VIII proclaimed hemp to be a sacrament for satanic rituals, and forbade its application by herbalists.[8] Most Renaissance-era

references to cannabis mention the plant in reference not to its healing or intoxicating properties, but as a cheap, reliable material for making paper, rope, or textiles—particularly canvas for sails. The plant only started to make a comeback in the sixteenth and seventeenth centuries, when European settlers began to grow it methodically and in large quantities in colonies around the world. This included North America, where cannabis was brought by European arrivals to Jamestown, between 1611 and 1762. George Washington also grew hemp on his farm, between 1745 and 1775.

In the 1830s, an Irish doctor named William O'Shaughnessy "discovered" the potential benefits of marijuana while teaching in India, at the Medical College of Calcutta. After conducting tests on animals, he eventually began recommending it for pain and muscle spasms, and for the often-fatal vomiting and diarrhea associated with cholera.[9] When the British convened the first Indian Hemp Drugs Commission between 1893–1894, hundreds of doctors from both continents came forward to testify for its utility in treating chronic and acute pain, cramps, headache, diabetes, asthma, impotence, and appetite loss.[10] They also found encouraging results in the treatment of rheumatism, rabies, cholera, tetanus, cramps, and delirium tremens.[11]

Marijuana was added to the third edition of the *Pharmacopeia of the United States* in 1851. The first American conference on the applications of medical cannabis was held by the Ohio State Medical Society, in 1860, with doctors discussing the herb for addressing a variety of problems, including chronic cough and gonorrhea.[12] In 1889, Dr. Edward A. Birch wrote a highly influential article in *The Lancet* discussing the use of cannabis for patients who had become addicted to opioid pain medications.[13]

At the start of the twentieth century, cannabis was a common treatment on both sides of the Atlantic for patients suffering whooping cough, asthma, chronic pain, and difficulty sleeping. On a smaller scale, it was also prescribed for stomach and gastrointestinal disorders, depression, diarrhea, anorexia, itching, bleeding in the womb, Grave's disease, and malaria.[14] Medical preparations involving cannabis such as Cannabin—marketed by the brothers T. and S. Smith in Edinburgh, Scotland—were being mass-produced, and widely available. Pharmacologist Emil Bürgi, at the Pharmacological Institution of the Bern University, in Switzerland, developed one of the most renowned cannabis research laboratories in Europe, and the firm of Hoffmann-La Roche & Co. patented a process to extract the potent ingredients in cannabis indica in 1914.[15] No such product, however, made it to the market.

There are many explanations for why research into medical cannabis began

to stall at this point.[16] In some cases, the herb was simply outmoded and replaced by other treatments that were more effective: vaccines and antibiotics, for example, were increasingly available for infectious diseases, while aspirin proved a far cheaper and easier drug to mass-produce than analgesics derived from plants. Furthermore, substances such as chloral hydrate, paraldehyde, sulfonal, barbiturates, and bromural seemed to have advantages over cannabis in the treatment of sleeplessness or pain.

In addition to this, the Western medical community became more skeptical of the approaches to herbal medicine brought forward by Samuel Thomson, Alva Curtis, and Dr. Benedict Lust. This skepticism was enhanced after the Carnegie Foundation commissioned Dr. Abraham Flexner to conduct a book-length survey of medical schools in the U.S. and Canada. The *Flexner Report*, published in 1910, was highly critical of the schools and colleges that sought to legitimize herbal and alternative medicine, arguing that they lacked the appropriate "laboratories and texts," and should be defunded or shut down.[17]

At the same time, ideas about the social and cultural harm of intoxicating substances had begun to shift in favor of prohibition. Cannabis was more or less lumped in with other vices as an engine of criminality and mental illness, and increasingly associated with the low morals and risky behavior of musicians and artists. In 1911, it was made illegal in the Commonwealth of Massachusetts, along with liquor, prizefighting, gambling, and prostitution.[18]

Even as 60,000 pounds of marijuana were being grown for medicinal purposes in 1918, and made available for purchase by firms such as Parke-Davis and Eli Lilly, the tide continued to move.[19] [20] In 1937, with few institutions of herbal medicine still around to defend cannabis, U.S. Congress passed the Marijuana Tax Act, which placed restrictions on the production and sale of cannabis that effectively pushed the drug beyond the limits of legality—in a decision that overruled advice from the American Medical Association. Marijuana was removed from the *United States Pharmacopeia* before it was published in its twelfth edition in 1942. With the passage of the Controlled Substances Act of 1970, cannabis was classified as a Schedule 1 substance, the same status applied to heroin and methamphetamine. Of course, the story didn't end there.

Although federal law in the United States had placed marijuana in the most prohibitive category—based on the belief that it was harmful and addictive, and had no medical application—people continued using it, and in large numbers. Even as a "war on drugs" intensified during the last quarter of the twentieth century, Americans remained skeptical of a prohibition-style approach to

cannabis, and harbored doubts about its purported role as a catalyst for antisocial behavior, or as a "gateway" to more harmful illicit substances. This is to say nothing of the immense expenditures by law enforcement, the courts, and the corrections system that were needed to try and eradicate a drug whose toxicity thresholds were unknown, and which had never been associated with an overdose. To cover the massive cost of criminalizing a substance that millions of otherwise law-abiding people used, it seemed worth asking whether other, more pressing social ills were going unaddressed: In 2017, for example, a report published by the FBI's Uniform Crime Reporting (UCR) Program indicated that more people had been arrested for marijuana possession in the previous year than for murder, rape, aggravated assault, and robbery—combined.[21]

Reports like these have regularly spurred calls for a reevaluation of the country's moral, cultural, and medical priorities. In fact, the conversation that has been going on since at least the 1970s, when an activist named Robert C. Randall persuaded a Superior Court Judge that the marijuana plants found on his porch in Washington, D.C., helped alleviate his glaucoma symptoms. After Randall subjected himself to a series of tests by scientists at UCLA, the possession charges against him were dismissed, and the Food and Drug Administration permitted him to access small amounts of cannabis grown in a facility at the University of Mississippi.[22] In the 1980s, the FDA approved the release of dronabinol and nabilone, two synthetic drugs, which mimicked the chemical behavior of THC, following significant findings into the uses of cannabis by cancer and AIDS patients.

In 1996, California moved to permit the sale and use of cannabis for medical purposes, under the Compassionate Use Act. Thirty-three states have since followed suit, so that nearly 60% of the U.S. population now lives in a state where medical marijuana is legal and regulated. Though cannabis has still not been rescheduled at the federal level, in 2014, Congress passed the Rohrabacher-Farr amendment, which limited the federal government from enforcing restrictions on cannabis in states where it had been legalized.

In a sense, prohibition may turn out to be just a brief phase in humankind's centuries-long relationship with cannabis. Notwithstanding the legal climate in the United States, research into the substance and its medical applications marched onwards throughout the twentieth century. Beginning in the 1960s, the Israeli organic chemists Raphael Mechoulam, Yechiel Gaoni, and Yuval Shvo succeeded in determining the essential properties of active compounds found in marijuana, most notably THC, cannabidiol (CBD), and cannabinol (CBN).[23] In the 1990s, a group of molecular biologists, led by Lisa Matsuda and Sean

Munro, effectively identified and cloned the cellular receptors that were activated by these same ingredients. A British team, led by pharmacologist Roger Pertwee, went on to reveal the existence of an entire endogenous cannabinoid system—a network of chemical messengers and receivers that uphold the body's natural ability to heal itself and maintain its essential functions. It now appears that cannabis fits into this system like a lock and key.

New avenues of research and exploration into the endogenous cannabinoid system are opening up every day. In the twenty-first century, our understanding of cannabis and its effect on human health has developed at a rapid pace, so that we are now able to track the individual pathways of the active ingredients in cannabis, as well as the ways in which they play off and complement each other. (This phenomenon is known as the Entourage Effect, and is discussed later in the book.) It's been exciting to see what the medical community can do with this windfall of knowledge, and, as a clinician, I've been grateful to witness firsthand how it can help patients and improve their quality of life.

2

THE ENDOCANNABI NOID SYSTEM

When explaining how cannabis might fit into a patient's treatment plan, the first thing I tend to cover is the human endocannabinoid system (ECS). Whereas plant cannabinoids might refer to active ingredients in a cannabis plant, such as THC or CBD, the ECS is a signaling system that operates naturally in every organ and tissue in our body—hence the prefix *endo-*, which means, "from within."

Even in people who have never consumed cannabis, the ECS plays a crucial role in maintaining *homeostasis*. It is a source of balance, in other words, and helps to stabilize the various physiological processes that keep us alive, including when we are enduring stress, injury, or illness. Inflammation, for example, is a completely normal response to tissue that is damaged, infected, or irritated. It's an essential mechanism, but it must be regulated closely; if it's too low, an unwelcome microbe might continue to thrive, while if it is too high, it could damage healthy cells. For an ailment like Crohn's disease, which involves the excessive inflammation of the intestinal lining, engaging the ECS can help to bring inflammation down to a more appropriate ("homeostatic") level.

The ECS works in virtually every organ in the body: preserving our nerves (neuroprotection), guarding healthy cells against injury (cytoprotection), modulating our immune system, and blocking the development of certain types of cancer. It provides essential support to memory and motor function, regulating pain, maintaining proper blood pressure, supporting healthy bone growth, and aiding the digestive system. (Backes) In addition to this, the ECS helps to regulate the processes that make up human metabolism, including energy intake, nutrient transport, lipid breakdown, and energy storage.

All of this takes place at the cellular level, and involves the three main actors that comprise the ECS: *receptors*, *neuromodulators*, and *enzymes*.

Receptors are proteins found on the semi-permeable surfaces of our cells.[24] In general, their effect on a given physiological process is determined by the type of cell where a receptor is expressed: receptors found in brain cells, for

example, interact with neurological function, while receptors on intestinal cells interact with digestion, and so on. Interestingly, one place where cannabinoid receptors are not found is the brain stem, which is responsible for breathing and respiration, and where opioid receptors, by contrast, are relatively abundant. As a result, an opioid overdose could do a great deal more to interrupt someone's vital functions than cannabinoids ever could. This is one way of explaining why cannabinoid overdose is virtually impossible; it's also why cannabis might be included in opioid withdrawal or replacement therapies.

On the surface of a cell, cannabinoids may dock with serotonin receptors (5-HT), vanilloid receptors (TRPV), or peroxisome proliferator activated receptors (PPARS). The most closely-studied cannabinoid receptors, however, are simply called cannabinoid type-1 (CB1) receptors and cannabinoid type-2 (CB2) receptors.

CB1 receptors are primarily located in the nervous system, including the brain, spinal cord, and peripheral nerve cells. They are essential for our basic cognition and motor functions, and have a role in storing memories and regulating mood, as well as transmitting sensations of pleasure or pain. In the basal ganglia, a region of the brain associated with voluntary motor skills and habitual memories, CB1 receptors might be involved in the process of learning to ride a bike or play a musical instrument.[25] CB1 receptors also have a role in inhibiting neural inflammation, and have been shown to dampen a nerve cell's excitability—potentially protecting brain tissue from excessive stimulation. Given these properties, the work of CB1 receptors have been of particular interest to researchers looking at conditions related to neural "excitotoxicity," including spinal cord injury, multiple sclerosis, and Parkinson's disease, as well as various neuropathies.

CB2 receptors are found to a lesser degree in the nervous system, but they are densely distributed throughout the spleen, tonsils, and thymus gland, and have a profound effect on the functioning of the immune system. These receptors have a crucial role in the body's response to infection, including regulating pain, and helping to control the release of proteins called cytokines, which are linked to inflammation.[26] In the presence of cancer cells, CB2 receptors can tear away the cloaking that makes those cells invisible to the immune system, and prevents them from multiplying and spreading.[27] CB2 receptors in bone cells, meanwhile, have been linked to maintaining bone density and stimulating growth, and may therefore have a part in reversing the effects of osteoporosis.[28] They are also found in gastrointestinal tissue, and can help to regulate inflammation in the digestive system. With this in mind, it may come as no surprise that cannabis

therapeutics which target the CB2 receptors have shown a lot of promise for the treatment of several inflammatory conditions, including arthritis, inflammatory bowel disease, and for several ailments of the immune system.

When a signal is carried from one cell to another, cannabinoid receptors are activated by compounds called *neuromodulators*. The two most abundant endocannabinoid neuromodulators are anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), which were discovered in the 1990s by Raphael Mechoulam and his colleagues at their lab in Israel. In general, AEA has a greater affinity for CB-1 receptors, and is both less potent and more discriminating than 2-AG, which has a greater affinity for CB-2 receptors, but they are each capable of activating both receptor types.[29]

Both AEA and 2-AG are synthesized in nerve tissue, in the space between nerve endings called the *synaptic cleft*. Unlike most neurotransmitters, which carry a signal from the presynaptic (former) to the postsynaptic (latter) nerve cell, these two messengers are instead sent to receptors on the presynaptic nerve cell. (Such a "backwards" action is often referred to as *retrograde transmission*.)[30] In the brain, if one neuron is overwhelming another with electrical activity, then the target neuron might respond by releasing AEA or 2-AG back into the synaptic cleft, to the source neuron, thereby slowing the release of more common neurotransmitters such as norepinephrine, serotonin, dopamine, or histamine.[31] In this way, endocannabinoids take part in a kind of negative feedback loop, allowing neurological function to regulate and fine tune itself.

In addition to their help with excitotoxicity, AEA and 2-AG can also attach themselves to CB2 receptors in brain cells called microglia. Unlike neurons, these brain cells patrol the brain for unknown pathogens, and in the presence of an intruder, they can help to mount an inflammatory response against it. These receptors, in turn, cause the synthesis of greater amounts of AEA, which brings inflammation back down. Glial cells are essential for energy production, network coordination, and synaptic plasticity, and they couldn't communicate with other brain cells without cannabinoid receptors.

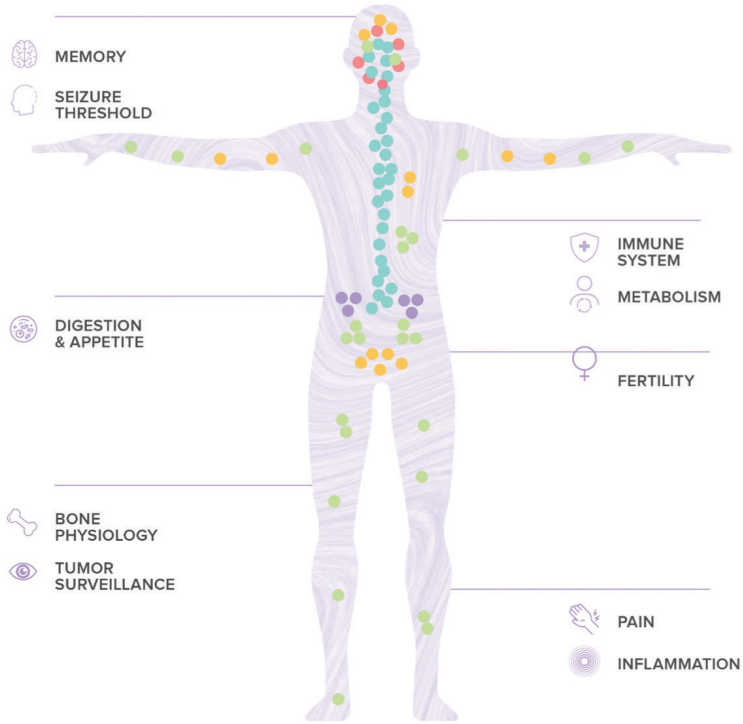
The third main actors in the endocannabinoid system are *enzymes*. AEA and 2-AG are "on demand" substances, which exist as common, spare molecular parts in the synaptic cleft. During times of stress, illness, or injury, cannabinoid receptors increase in the central nervous system or in other organ systems in the body, and it falls to nearby enzymes to either build these endocannabinoids up or to break them down. DAGL-α and DAGL-β are the enzymes involved in the synthesis of 2-AG, and NAPE selective phospholipase-D helps to synthesize

AEA. Conversely, MAGL is the enzyme involved in the breakdown of 2-AG, whereas FAAH is involved in the breakdown of AEA.

In basic terms, cannabis has the effects that it does because of the way it can interact with these three actors in the ECS. Anandamide, for example, has been shown to fold over on itself in such a way that it resembles THC in three dimensions; when THC enters the brain from the bloodstream, it takes the place of AEA by attaching itself to the CB1 receptors on nerve cells. As it happens, CB1 is the only cannabinoid receptor responsible for the euphoric and "high" feeling associated with cannabis; because of its affinity for both plant-derived cannabinoids (like THC) and endogenous cannabinoids (like AEA), the two cannabinoids can have the same effect on the nervous system. Runner's high, for example, is a euphoric feeling brought on during exercise, which people in the past have attributed to the release of endorphins in the brain. Recent studies, however, have indicated that this euphoria may be brought on by the activation of the CB1 receptor, which induces increased levels of AEA during a workout. As it turns out, the effect of runner's high may have nothing to do with endorphins, but might instead be the result of an abundance of AEA, which functions as our body's own "natural THC."

Plant-derived cannabinoids can also directly affect the enzymes responsible for the synthesis or breakdown of neuromodulators. CBD, for example, has been shown to reduce FAAH expression in inflamed intestinal tissue, in turn reducing the amount of AEA that is broken down, so that a greater number of CB2 receptors are activated. It may therefore have promise for reducing inflammation-induced intestinal hypermotility in patients with irritable bowel syndrome.[32] Meanwhile, a study of genetically-constipated mice showed their guts could be brought to normal motility when they were treated with cannabinoids that inhibited DAGL-α: less 2-AG was synthesized, and so fewer CB1 receptors were activated, which meant fewer cells in the intestine released acetylcholine—a compound which decreases smooth muscle contractions in the digestive tract.[33]

In the years to come, therapies involving cannabis will be made more effective as pharmacologists are able to better pinpoint the elements in these complex processes, step by step. The more we improve our understanding of cannabinoids and their interaction with the ECS, the better our patient outcomes will be.



Targets

- Cannabinoid Type 1 *(CB1)*
- Cannabinoid Type 2 *(CB2)*

Receptors

- Serotonin Receptors *(5-HT)*
- Vanilloid Receptors *(TRPV)*
- Peroxisome Proliferator Activated Receptors *(PPARS)*

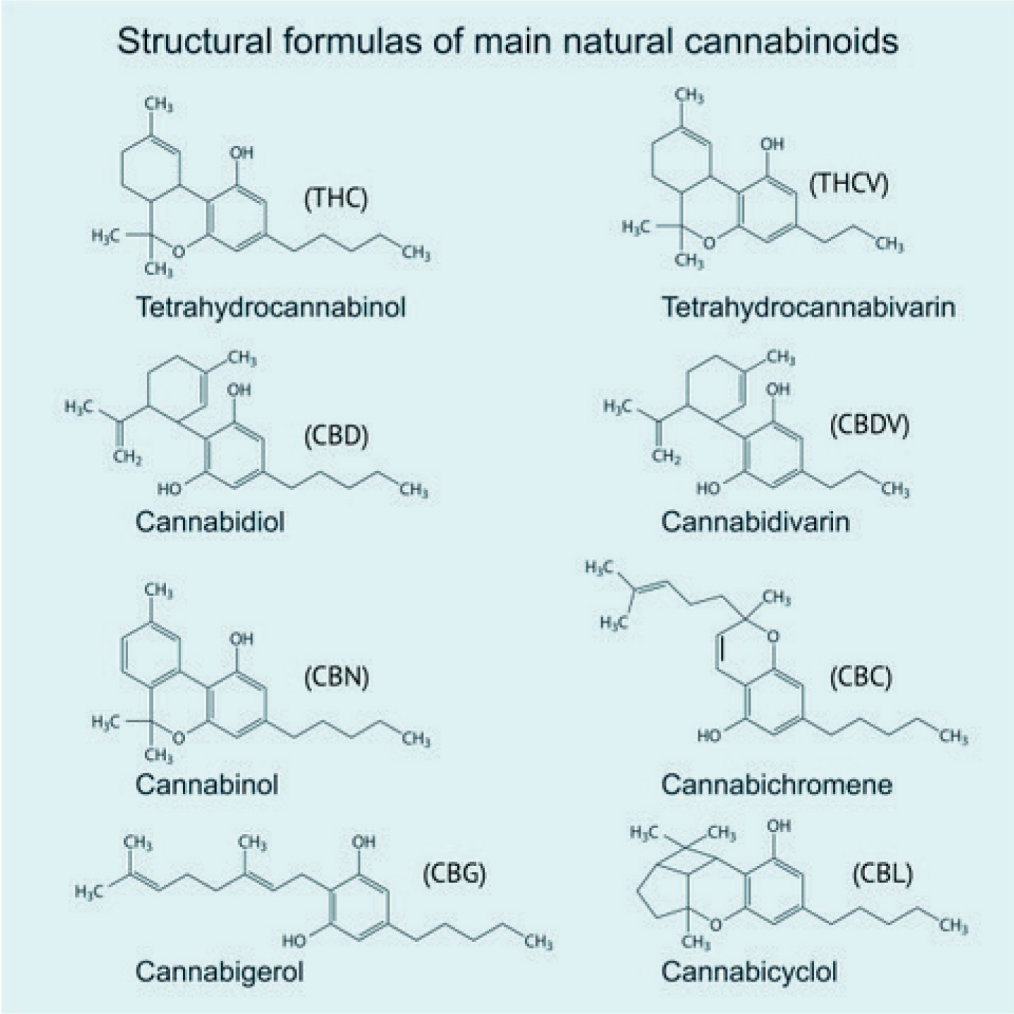
3

THE CANNABI S PLANT, ITS CONST ITUENTS, AND THE ENTOUR AGE EFFECT

The more you read about the human endocannabinoid system, the more it becomes clear that cannabis, itself, is not a blunt instrument. It is a highly delicate and sophisticated organism, with vital systems that have been honed over centuries of natural selection. And notwithstanding the immense usefulness of the cannabis plant for our own purposes, the plant's fossil record actually predates the arrival of *Homo sapiens* by about twenty million years. What this means is that the active compounds that have been identified in cannabis, which number over 100, almost certainly serve a purpose besides human medicine.

Some cannabinoids, for example, have herbicidal properties, which cause the plant to prune its lower leaves as it matures. This allows more energy and biomass to go into reproductive functions, which are served by the flowers and seeds. Other cannabinoids have the potential to block ultraviolet radiation, which could damage the plant's DNA, and affect its ability to reproduce. Still other cannabinoids may alter the smell or taste of the cannabis flower, to make them more attractive to cross-pollinators. Or they may have pesticidal properties—the sticky trichomes found in cannabis, for example, have been known to trip up predatory birds and insects.

For the purposes of this book, I'd like to focus on three main compounds produced by the cannabis plant: *phytocannabinoids*, *terpenes*, and *flavonoids*.



Phytocannabinoids are bioactive compounds that are unique to the cannabis plant. They were first identified and isolated by Raphael Mechoulam and his colleagues in the 1960s, and since then, most studies into medical cannabis have investigated their interactions with the human body. The overwhelming focus in this research has been on *tetrahydrocannabinol* (THC), the chief psychoactive cannabinoid, whose effects are mediated through CB1 receptors in the nervous system. *Cannabinol* (CBN), meanwhile, is an oxidative product of THC, and an agonist of CB1 and CB2 receptors, which has shown promise from in vitro tests as an anticonvulsant, an anti-inflammatory, and an inhibitor to keratinocyte proliferation associated with skin disease. There is also substantial evidence that it can stimulate mesenchymal stem cells, causing increased bone formation within marrow. More recent investigations have gone into the behavior of *cannabidiol* (CBD), which has a low affinity for CB1 or CB2 receptors in the

nervous or immune systems, but which has shown to work as an antagonist for these receptors, binding to them and thus dampening whatever signal those cells carry.

A somewhat lesser-studied cannabinoid is *cannabichromene* (CBC), a known anandamide uptake inhibitor that has been recognized for its antibiotic, antifungal, and anti-inflammatory properties, as well as for its possible cytotoxicity against certain cancer cells, and as an effective treatment for depression. One other phytocannabinoid worth mentioning is *cannabigerol* (CBG), a weak agonist for CB1 and CB2 receptors, which has applications for spasticity, erythema, certain fungal infections, depression, and hypertension, in addition to its cytotoxicity to human epithelioid carcinoma, and to human breast cancer cells. Like THC, it has also shown to be an inhibitor for keratinocyte proliferation, and as an antibiotic against MRSA, a harmful bacterium. Lastly, the cannabinoid *tetrahydrocannabivarin* (THCV), a CB1 antagonist, has been shown to reduce appetite and lead to significant weight loss, reduced body fat, and lowered leptin concentrations in obese mice. Rat models have also demonstrated some anticonvulsant properties in THCV, as well as a decrease in hyperalgesia and inflammation, with other possible benefits in bone formation and fracture healing.

Terpenes and *flavonoids* are compounds that have a role in determining the color, flavor, and aroma of a given cannabis sample. They are common in other flowering plants, typically developed to dissuade predators, or to improve the likelihood of pollination by producing attractive flavors and smells. It's usually pretty easy to determine what kind of sensory effect a terpene or flavonoid carries based on its name: limonene, for example, tends to have a citrusy odor that might remind you of lemons, whereas pinene usually accompanies the smell of coniferous trees. But their benefits go way beyond being pleasing to the senses: citrus essential oils containing limonene, for example, have been effectively used in treatments for anxiety by increasing serotonin levels in the prefrontal cortex.[34] The terpene myrcene has also been extensively shown to have sedative properties, which may go some way in explaining the "couch lock" effect of several cannabis strains.[35]

You may notice that I haven't mentioned many of the individual effects of either cannabinoids, terpenes, or flavonoids up until now. This is because over the years, pure samples of cannabinoids such as THC have had a far lesser effect than extracts with a broad profile of ingredients. (An early sign of this phenomenon was detected in the 1980s, after the FDA approved a drug called dronabinol—a synthetic form of THC, marketed as Marinol—whose effects

against nausea or anxiety never worked as well as whole-plant medication.) Cannabis, it seems, is a substance that seems to work better in its natural form than any single component being isolated and taken on its own.

Together, the full ensemble of cannabinoids, terpenes, and flavonoids seem to complement each other, working through multiple receptors at once, and often enhancing each other's signals to the body. Often, cannabinoid receptors can play against each other, or have inverse effects on the body: CB1 receptor activation, for example, promotes increased blood lipid levels and liver fibrosis, while CB2 receptors decrease blood lipid levels, fibrosis, and liver inflammation. CB1 and CB2 receptors are also believed to have opposite effects in cardiac tissue, and in muscle fibers, where CB1 and CB2 receptors can either promote or inhibit energy use.

This synergistic quality of the active ingredients in cannabis is referred to as the Entourage Effect. In almost every way cannabis has been used, it's possible to see the Entourage Effect at work.

One example might be found in topical creams derived from cannabis extracts. On its own, CBD has been known to block the synthesis of oils produced by sebaceous glands in the skin, which are stimulated in the presence of the modulator AEA. At the same time, essential oils containing terpenes, such as linalool and limonene, have been shown to inhibit the growth of the bacterium *Propionibacterium acnes*. Together, the three ingredients work from multiple directions to prevent the inflammation associated with infected pores, and can form a powerful mediation against acne.

Another example is in the use of cannabis for psychiatric disorders. Whereas pure THC lacks conclusive support for its efficacy as a treatment for depression, CBD shows a great deal more promise, in part because of its ability to activate serotonin 1A receptors in the brain.[36] Given the anti-depressive potential linked to limonene and linalool (a terpene also found in lavender), a cannabis-based treatment that was low in THC—but in which CBD and these terpenes predominated—could be highly effective.

I've sought to take full advantage of the Entourage Effect in my own work as founder and CEO of Reserve:MD™. When developing a product, I begin by getting a qualitative analysis of the strain of cannabis being used, so that I can understand its full profile of cannabinoids and terpenes, and the ratio of these compounds to one another. In many cases, I will then tinker with these ratios, so that these ingredients can be made to work in synergy: adding terpenes like beta-myrcene or linalool, for example, may make for a more sedative product, whereas limonene could make a product more uplifting and invigorating.

Historically, people have believed that these qualities could be pinned down

simply by identifying the species involved—that is, by assuming that a *cannabis sativa*-derived product would be more energizing, or believing that a *cannabis indica* product was more likely to put you to sleep. As our understanding of the plant has improved, however, this distinction has lost a lot of its relevance. It's now believed that *sativa* plants have simply tended to bear a greater amount of terpene compounds with elevating qualities, while *indica* strains have had higher levels of more sedative terpenes. In a few years, these generalizations may themselves fall apart, so that people will stop talking about species entirely, and focus much more on the unique plant compounds in a given product. The cannabinoid and terpene profile are what really matters; I believe that as selective breeding methods improve—and it becomes easier to isolate the essential oils with the qualities we want—it will be possible to customize individual medical cannabis products to deliver the optimal effect.

Commonly Found Terpenes in Cannabis

	BENEFIT	AROMA	ALSO FOUND IN
 *Pinene*	Anti-Inflammatory† Antibacterial† Bronchodilator† Aids Memory† Alertness† Increased Energy† Antiseptic†	Pine Earth	Pine Trees Rosemary Sage
 *Myrcene*	Analgesic† Sleep Aid† Muscle Relaxant† Anti-Inflammatory†	Flowers Pungent Earth	Mango Lemongrass Hops Thyme
 *Limonene*	Treats Acid Reflux† Stress Relief† Elevated Mood† Anti-Inflammatory† Antiseptic†	Citrus Fresh Spice	Lemons Oranges Juniper
 *Linalool*	Anesthetic† Analgesic† Stress Relief† Elevated Mood†	Flowers Lavender Citrus Fresh Spice	Lavender
 *Terpineol*	Calming Aid† Antibacterial†	Pleasant Lilac Citrus Wood	Mugwort

†These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Caryophyllene

Anti-Inflammatory†
Analgesic†
Protects cell lining†
Digestive Tract†
Antiseptic†

Citrus
Spice
Pepper
Wood

Black Pepper
Cotton
Cloves

Humulene

Anti-Inflammatory†
Analgesic†

Pleasant Lilac
Citrus
Wood

Basil

Terpinolene

Antioxidant†
Antibacterial†
Stress Relief†

Pine
Herbal
Anise
Lime

Coriander

Ocimene

Decongestant†
Antiseptic†
Antiviral†
Bactericidal†

Citrusy green
Wood
Tropical Fruit

Thyme
Alfalfa

†These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

4

ROUTES OF CONSUMPTION

There are many ways patients involving cannabis in their treatment plans can decide to consume it. Besides smoking or vaporizing, patients can take tinctures containing cannabis extracts, swallow capsules or foods that have been infused with cannabis oils, use creams containing cannabis for their skin, or apply suppositories containing cannabis.

As you can imagine, the most common and traditional route of administration is smoking. Patients can roll cannabis into a "joint" using cigarette papers; pack cannabis into a wood, glass, or ceramic pipe; or smoke it from a "bong," a device in which the pipe bowl is attached to a water-cooling chamber. Whatever method you prefer, one advantage of smoking is that it always gives you the full terpene and cannabinoid profile—since the plant has not been broken down in processing, you have access to all of its potential benefits. Compared to other consumption methods, smoking is also generally seen to provide the highest *bioavailability* of cannabis; between 20% and 50% of the active ingredients remain unchanged when they reach the bloodstream and prompt a response.

Another advantage of smoking is that it works quickly. People who smoke cannabis usually begin to feel the effect within ninety seconds, and experience a peak within fifteen to twenty minutes. (It wears off after two to three hours.) This makes the substance easy to titrate in small "sips"; the average inhalation will provide one to ten milligrams of cannabinoids, depending on the potency of the product, the length of inhalation, and the surface area of the user's lungs. If a patient isn't getting relief after fifteen to twenty minutes, and isn't getting too "high," then they can simply take a bit more.

The disadvantages of smoking are fairly obvious: you're burning something, usually at 460 degrees Fahrenheit or above, and by inhaling the smoke, you expose yourself to all of the carcinogens and toxins that go along with the process of combustion, including carbon monoxide, benzene, and toluene. On one hand, higher rates of lung cancer or pulmonary disease have not been shown

in people who begin smoking marijuana, in comparison to people who don't. In theory, this has to do with some of the protective effects of certain cannabinoids: some of these have anti-inflammatory or anti-carcinogenic effects, so that when you inhale cannabis, you're also stimulating an immune response that will recognize the harmful elements of smoke.

On the other hand, as a doctor, I still have trouble telling people that it's a good idea to draw carcinogens into their lungs. Because of this, I very rarely recommend people smoke marijuana flower whole. To those who do smoke, there are a few things I recommend people do to mitigate the risks: for example, I discourage the use of lighters, which usually involve propane or butane fuel, and whose fumes are harmful to inhale. An alternative is to use a light hemp wick, which has a much cleaner flame.

For people who still want to use cannabis, and avoid combustion, another method they might consider is herbal vaporizing. This method works by heating up ground flower at a carefully-calibrated temperature—usually between 260 and 460 degrees Fahrenheit. This is high enough to release the active ingredients in cannabis oil, but not so hot that the cannabis combusts. The cannabis doesn't burn, in other words—it smolders, and can be drawn into the lungs in a way that bypasses the potential carcinogens in smoke, as well as the fumes from propane or butane lighters.

Herbal vaporizers are operated through one of two mechanisms: conduction and convection. In conduction vaporizers, cannabis is placed directly on a heating element—usually a piece of metal or coil of wire—and, as a result, a moderate amount of combustion still occurs. Users can avoid this small-scale combustion by using convection vaporizers, which reduces the possibility of combustion by subjecting the cannabis to air that has been heated up from another chamber. The design is a little bit like a hair drier; a disadvantage of convection vaporizers is that they are heavier and less portable than conduction vaporizers, but by blowing a gust of hot air past the cannabis—instead of cooking the cannabis on a solid heating element—they make for a much purer and cleaner form of pulmonary ingestion, without the other byproducts.

One drawback of vaporization is that it may not sterilize cannabis the same way combustion will. As a result, it may potentially expose the user to the effects of mold and bacteria. The most obvious way around this is for patients to always seek out a clean cannabis product, and make sure that the marijuana they buy has been properly cured and dried.

After burning or herbal vaporizing, the next most popular route of administering cannabis is through the use of oil. On the whole, cannabinoids are lipophilic, meaning the active ingredients tend to dissolve in fats, unlike

hydrophilic compounds, which dissolve in water. Oil vaporizers work somewhat like herbal vaporizers, except that instead of heating up the raw herbs, they heat up a lipid-based solvent—usually a cartridge, containing a small amount of cannabis-infused oil. Their mechanism is comparable to an electronic cigarette, and allows the user to inhale heated vapors and pull cannabinoids into their lungs, without smoke or combustion.

For patients who are considering vaporizing oil, I have a few words of advice. Firstly, it's very important that cannabis oil comes from a reputable source, and is tested by a third party, so that the product can be analyzed for traces of chemicals such as pesticides, herbicides, or residual solvents, which might have been left behind from the growing or manufacturing processes. Several methods of cannabis oil extraction involve butane or propane, which are toxic, and so it's important to choose a product from which these have been completely removed.

Another concern when choosing products with cannabis oil is the additives that might be involved. Because raw cannabis oil is very thick, and can be pretty challenging to vaporize through conventional apparati, lots of manufacturers will dilute it with something less viscous. Often, they will use a thinning agent such as propylene glycol, which is a common stabilizer, emulsifier, or thickening agent for processed foods. Because the FDA has deemed propylene glycol to be Generally Recognized as Safe (GRAS), many manufacturers have reasoned that it is appropriate not only for oral consumption, but for also inhalation. I think this is a serious mistake; a known product of heating propylene glycol is formaldehyde, a substance used in embalming fluids, which has been linked to an increased risk of leukemia and nasopharyngeal cancer. (NCI) For this reason, I always stress that people visiting dispensaries and choosing a cannabis oil product avoid anything made with propylene glycol.

Vaporizers can also be designed for consuming oils with a more concentrated cannabis extract. These products are sometimes called shatter, crumble, wax, and dab, and can be appropriate for treating severe medical conditions. I don't have any objection to the use of these, but I do ask that patients who buy them be mindful of two things: firstly, as mentioned above, it is imperative that they choose a product made without herbicides or pesticides, since these toxins—like the cannabis extract itself—will be highly concentrated. Secondly, given the high potency of shatter or wax, one should exercise extreme caution when setting dosage levels. The effect from even a pinpoint-sized dot can be overwhelming, and so I recommend patients start with a very small amount, and adjust a little bit at a time.

Another way of consuming cannabis is in the form of edibles, which can fall

into one of two main categories: pure edibles and tinctures. In a tincture, dried cannabis has been immersed in a solvent, such as food grade alcohol, which causes the cells in the flower to swell and break open, releasing active chemicals into the mixture. This solvent, in turn, can be placed under the tongue, which allows the cannabinoids to enter the bloodstream through the mucous membranes. In this method, users will start to feel the effects within fifteen to twenty minutes. These will peak after about an hour, and then wear off after three or four hours.

It's also possible to simply swallow a tincture containing cannabis oil, or to infuse it with honey or a high-fat food, such as cookies, brownies, or chocolates. In this case, it is the gastrointestinal system that guides cannabinoids into the bloodstream, rather than the lungs or the mucous membranes. It's worth keeping in mind that the bioavailability of cannabinoids in the gut can range between 5% and 20%; moreover, edibles are by far the slowest route of administration—the effects take up to two hours, and last from six to eight hours.

Edibles can also deliver a different set of compounds in the bloodstream than smoking or vaporizing. Whenever you swallow something, it goes into your gastrointestinal tract, and is processed by your liver. During this process of filtering and metabolism, the liver often converts food or medicine into other by-products, before the raw substances are allowed into the bloodstream. Fifty percent of THC, for example, is likely to be converted into 11-OH-THC, a smaller molecule that crosses the blood-brain barrier much more extensively, and is up to four times as psychoactive of THC. Some users find this overwhelming, especially given how long the effects can last. (You may have heard of someone having a bad experience after eating a "pot brownie.") People who are more prone to the unpleasant side effects of cannabis, such as anxiety psychosis—or who don't want the feeling of euphoria—should therefore be careful about taking edibles made with psychoactive cannabinoids, including THC.

One other route of administration I recommend is through topical creams. I'd like to tread lightly with this category, since I'm closely involved in efforts to determine the efficacy of topical cannabis treatments, and the results so far have been mixed. Part of this has to do with the fact that our skin is an aqueous barrier, which makes it difficult for the mostlylipophilic active substances in cannabis to penetrate into deeper tissues. Oil and water simply don't mix, and so it's difficult to determine how cannabis can be absorbed through the skin into organs or muscular tissue. Frankly, despite the huge market for cannabis topicals for joint pain or muscle pain, most of the results are based on anecdotal evidence. Although patient reports have been very powerful, more evidence is still required to determine how well topical applications of cannabis truly work

for deep-tissue penetration. On the other hand, the skin itself is actually very rich in cannabinoid receptors, and members of the American Academy of Dermatology have endorsed the use of topical cannabis as an adjunct treatment in treating psoriasis, eczema, and acne, in recognition of its anti-inflammatory effect. For people suffering from these disorders, cannabis-infused creams may be a highly effective form of treatment.

Section II

CANNABIS FOR SPECIFIC AILMENTS

5

PAIN

Some of my earliest prescriptions for medical marijuana were for people suffering from cancer-related pain. In these cases, many of the patients I saw benefited from products that contained THC, but what impressed me the most was the amount of success patients reported with products containing only CBD, which is not associated with the euphoric "high" feeling. These outcomes convinced me that the benefits of cannabis were largely unrelated to the "high" associated with THC. I now recommend it for multiple forms of pain, including chronic back and neck pain, pain from inflammatory bowel disease, migraine headaches, neuropathies, and arthritis—to name just a few. In doing so, I've joined the millions of physicians worldwide who have applied cannabis for pain over the past 5,000 or so years.

Today, approximately one if four adults in Europe—and about 100 million adults in the United States—are affected by some form of pain. Pain motivates more than half of all physician visits in this country, and each year, over $600 billion in healthcare costs and lost productivity can be traced to the financial burdens of pain management. Of the twelve million people who have used cannabis therapies for pain, many have been able to forgo the use of other pain medications, some of which are highly addictive, and pose a much greater risk of overdose.[37] This represents a significant breakthrough for the country's opioid crisis, since the states that have passed laws permitting the use of medical cannabis have shown drastic declines in per capita opioid use, in addition to reduced incidence of opioid overdoses and opioid-related deaths.[38]

When considering cannabis-based treatments for pain, it's worth considering how pain works. Pain is often difficult to put into words, and deeply personal; not infrequently, ideas about pain are shaped through our own unique biology, the unique character of a given ailment, our personal experiences and temperament, and the society and community in which we live. Even the most articulate descriptions of physical pain usually fall short to capture how much impact it has, or the degree to which severe or chronic pain can take over our

lives, and the lives of those around us.

Keeping this in mind, the most objective categorizations of pain come from doctors, who tend to divide pain into four types: nociceptive pain (a response to damaged tissue), neuropathic pain (a response to directly-damaged sensory or spinal nerves), centralized pain (the result of pain signals being improperly amplified), and inflammatory pain. The last of these, inflammatory pain, is associated with pathways of the immune system, and so I've set aside my discussion of it for Chapter 6.

Nociceptive pain is caused by external pressure, cold, heat, or from internal trauma, stimulated by the release of compounds like bradykinin, prostaglandins, or leukotrienes. It might be detected in sharp, aching, or throbbing sensations, and its main purpose is to alert us to the fact that we are wounded or hurt. Neuropathic pain, by contrast, is caused by direct damage to sensory or spinal nerves, which allow aberrant pain signals to be sent to the brain. A classic example of this is diabetic neuropathy, wherein chronic elevations in blood glucose cause injury to peripheral sensory nerves, so that the nerves fire abnormally. Centralized pain, as the name implies, is caused by an internal dysfunction of the central nervous system. It may lack a clear peripheral cause, and simply result from the amplification of an existing pain signal, so that it becomes impossible to ignore. A common example of this form of pain is fibromyalgia.[39]

Cannabinoids may have a role to play in mediating all three of these types of pain ailments. This begins when tissue is damaged, which prompts the release of various neurotransmitters, including histamine and serotonin, as well as elevated levels of tumor necrosis factor alpha, interleukin 1 beta, interleukin 6, and interleukin 17. While it might be difficult to explain how these compounds are synthesized, received, and broken down or repurposed, what's most important to understand is that endocannabinoids such as AEA and 2-AG are present in the same circuits where these neurotransmitters go to work—particularly in the brain, spinal cord, and dorsal root ganglion.[40] By binding to the CB1 receptors on a nerve cell that is sending a pain signal, cannabinoids have the power to attenuate that signal by slowing down the release of those neurotransmitters. This process can take place locally in the tissue that has been traumatized, though cannabinoids can also inhibit the conduction of pain in the dorsal horn of the spinal cord, and in the ascending spinothalamic tract.[41] Furthermore, cannabinoids such as anandamide can bind to CB2 and vanilloid receptors, and therefore do even more to inhibit the release of neurotransmitters associated with pain, such as GABA, from sensory neurons.

The potential role of plant-based cannabinoids in helping these processes along is of continuing interest. As of this writing, cannabis has been demonstrated to be an effective agent in pain management in 28 randomized control trials, 16 quality systematic reviews, and 21 primary research articles, wherein patients who smoked cannabis or took oral extracts found substantial relief from pain associated with a variety of illnesses, including neuropathy, multiple sclerosis, and rheumatoid arthritis, in addition to musculoskeletal pain, cancer pain, and pain induced by chemotherapy.[42] In view of this research, a report by the National Academies of Sciences, Engineering, and Medicine concluded that there is, "substantial evidence that cannabis is an effective treatment for chronic pain in adults."[43]

Using cannabis to reduce or remove opioids from someone's treatment plan often means they'll be less susceptible to the unpleasant side effects of opioids, which are burdensome in their own right. It's not unusual for patients taking opioids to suffer from nausea, vomiting, constipation, and urinary retention—ailments which may themselves require further medication to address. Moreover, it's worth remembering that the cognitive impairments associated with opioids—such as dizziness, drowsiness, or depression—can affect not only the person taking them, but can also make life more difficult for their families and close friends, especially in severe or terminal cases. When the opioids are taken out of the mix, a patient can often be more mobile, alert, and mentally present with the people who care for them.

"The reduction in opioids after medical cannabis was tremendous," Julia Arnsten, MD, MPH, the chief of general internal medicine at Albert Einstein College of Medicine, told *General Surgery News* in an article published in 2018.[44]

The potential for cannabis to take over the work done by other pain medications is particularly encouraging for anyone who cares about the epidemic of prescription opioid abuse. On average, more than 130 people in the United States die from an opioid overdose each day, and over two-thirds of drug overdose deaths in 2017 involved opiates such as heroin, fentanyl, and prescription opioid painkillers.[45] [46] All of this is brought to mind when reading a 2017 study from California, which surveyed 2,897 medical cannabis users. Of these subjects, 841 were opioid users, who told researchers they preferred cannabis-based drugs because they were more effective, and had far fewer adverse effects.[47] Another study looked at chronic pain sufferers who accessed a cannabis dispensary in Michigan: of the 244 subjects, 64% reported a decrease in opioid use, while 45% reported fewer side effects associated with medication,

and an improved quality of life.[48] Opioid addiction is a national concern, and medical cannabis may prove to be a highly effective tool in the fight against it.

6

INFLAMMATION

Inflammation is one of the most commonly-discussed ailments for which cannabis can be an effective treatment. It is also one of the most difficult to pin down, since inflammation almost never acts alone, and isn't even necessarily a sign of ill-health. In tissue that is infected or hurt, the redness, heat, swelling, or discomfort that accompany inflammation are altogether necessary to maintain homeostasis, but there are many conditions in which inflammation might signal that an immune system is overactive or otherwise dysfunctional.

To understand how the endocannabinoid system can keep the inflammatory response in check, it's worth explaining why and how inflammation occurs. This usually begins with the presence of an unknown pathogen, which triggers the release of bradykinin or histamine, hormones that are sometimes referred to as *inflammatory mediators*. This causes small blood vessels to become wider and less constricted, so that more blood can reach the injured or infected tissue, and for the affected area to become warmer to the touch. Under normal conditions, tissue that is warmer and more vascular can allow immune cells to migrate more freely, even as unwelcome viruses, bacteria, or fungi are broken down by the heat. Furthermore, inflamed mucous membranes are more likely to secrete saliva or phlegm, which makes certain pathogens easier to flush out.

Inflammation often goes hand in hand with fatigue. When the body is warmer and metabolism is higher, the immune system works harder and consumes more energy, as more immune cells and antibodies are produced, and this has a tendency to makes us feel tired and worn out. In addition to the swelling and compression of inflamed tissue, many inflammatory mediators can also irritate nerve cells, which cause more intense pain signals to be sent to the brain. Tendonitis (inflammation of the tendons), laryngitis (inflammation of the larynx), prostatitis (inflammation of the prostate), and dermatitis (inflammation of the skin) are all associated with high levels of discomfort, which do not subside until the infection is brought under control. More serious are ailments such as ulcerative colitis (a disease of the intestine), and vasculitis (a disease of

the blood vessels) are the result of certain inflammatory mediators being overexpressed, so that the immune system fights against the body's own organs, and often breaks down healthy tissue.

In many cases, imbalances like these can be brought back to normal through the endocannabinoid system. As a great deal of research has shown, cannabinoid receptors including CB1 and CB2 are expressed by cell groups involved in the immune system—such as lymphocytes, eosinophils, and basophils. At the same time, the ability of these cells to migrate or release certain inflammatory mediators can be inhibited by cannabinoids modulators such as anandamide (AEA) or 2-arachidonoyl-glycerol (2-AG).

One study from 2010 found that AEA can bind to CB2 receptors expressed by the CD4 class of lymphocytes, and inhibit them from releasing cytokines, which intensify the inflammatory response, including tumor necrosis factor alpha (TNF-α;), interferon gamma (INF-γ), and interleukin 17 (IL-17).[49] Another study, from 2008, indicated that both AEA and 2-AG could dock with peroxisome proliferator-activated receptors expressed on immune cells called splenocytes, which slow the release of interleukin-2 (IL-2), another cytokine associated with inflammation.[50] Still another study, from 2013, found that AEA binding on CB2 receptors of dendritic cells (a class of white blood cells) could reduce the release of interferon alpha (IFN-α), interleukin-6, and interleukin-12—which, again, are synthesized to promote inflammation.[51]

Though we've only just begun to appreciate how these processes work, the potential role of cannabis in treating inflammation-related symptoms is extremely compelling, especially when applied to autoimmune illness. For example, it may be possible to engage cannabinoids that dock with CB1 or CB2 receptors in cells on the outermost layer of the dermis, thereby reducing the inflammation associated with psoriasis, an autoimmune illness of the skin.[52] For patients diagnosed with autoimmune liver disease, including hepatitis and primary biliary cirrhosis, cannabinoids have shown a great deal of promise in reducing the release of inflammatory cytokines such by regulatory T-cells, which also express both CB1 and CB2 receptors.[53]

Arthritis

As the above examples illustrate, inflammation is both an ailment of its own, and a significant source of collateral pain and discomfort. This is hardly news to anyone of the 54 million Americans affected by arthritis. Of these, about three-

fifths suffer from osteoarthritis, which occurs when the cartilage surrounding bones and cartilage wears away due to overuse. Rheumatoid arthritis—an autoimmune condition, which affects the synovial membranes that cushion and lubricate our joints—is also a widespread concern.[54] Inflammation may be the most common symptom of these ailments, but it is hardly the only one: both conditions cause pain and swelling, and have the ability to stiffen movement, and reduce flexibility.

One of the reasons cannabis has been a useful ingredient in treatment plans for arthritis is because of what it can do for bone health. One example can be seen in a 2009 study of mice whose genes had been altered to remove the CB1 or CB2 receptors, and who developed signs of bone weakness that were far more pronounced than those in the control group.[55] The relationship between CB2 expression and bone disease has also been observed in humans, as in another 2009 study, which showed people with dysfunctional CB2 receptors to have significantly weaker hand bones.[56]

Perhaps even more important is the potential cannabis has shown for reversing the process that leads to inflammation in patients diagnosed with rheumatoid arthritis. One particularly interesting study found that cannabinoids could simultaneously reduce the secretion of cytokines involved in inflammation from one type of TH immune cells, which were being under-produced, and increase the type of TH immune cells that were scarce.[57] Another study, from 2006, found that transdermal applications of CBD to a sample of arthritic rats were successful in decreasing biomarkers including CGRP, a powerful vasodilator that can contribute to neurogenic inflammation.[58] Still another study, from 2003, found that plant-based cannabinoids could suppress the expression of interleukin-1beta—one of the most prominent markers for inflammation in patients with rheumatoid arthritis—by as much as 50%.[59]

It’s not hard to imagine what these findings might mean for clinicians. Indeed, a lot of contemporary research seems to confirm a quality in cannabis that has been observed by doctors for literally thousands of years: as pharmacists living in China in 2,000 BCE observed, in addition to addressing pain from rheumatoid arthritis, cannabis can also reverse the underlying dysfunction that causes it.[60] One study from 2005 examined 58 subjects with rheumatoid arthritis that had not been adequately addressed by standard medication, and found that those who took an oral-mucosal cannabinoid spray, in which THC and CBD predominated, felt significant reductions in pain on movement, pain at rest, and quality of sleep when compared with the control group.[61]

Most exciting of all is what plant-based cannabinoids can do for rheumatoid

arthritis sufferers who until now have been forced to take pain relievers like aspirin, ibuprofen, or acetaminophen, or more powerful immunosuppressants and anti-inflammatory drugs. The side effects of these treatments aren't always significant, though some non-steroidal antiinflammatory drugs (NSAIDs) have been shown to irritate the stomach or intestines, and there is a possibility of heartburn or indigestion, drowsiness, diarrhea, nausea, vomiting, or gastric ulcers, while longer-term doses of acetaminophen have been linked to some forms of kidney damage. Meanwhile, stronger painkillers—such as codeine, morphine, oxycodone, propoxyphene, or tramadol—can increase a patient's vulnerability to constipation, shortness of breath, and sedation, as well as serious dependence or addiction.

Immunosuppressants are a different story, in that their adverse effects are almost always disruptive, which is why they are usually only prescribed for serious inflammatory disorders. In addition to making patients more susceptible to infection, these drugs have been linked to higher exposure to cardiovascular disease and bone marrow suppression. Typical responses to steroidal anti-inflammatories such as prednisone are no less serious, and can include higher incidence of bruising and muscle weakness, hypertension, digestion problems, unusual weight gain, and elevated blood sugar.

To address the symptoms of rheumatoid arthritis, alternative treatments the potential to obviate the need for these other medications, and thus spare patients from their considerable downsides. A great deal of evidence has shown that cannabis can not only help counteract the cause of these ailments, but also reduce the quality-of-life issues associated with riskier anti-inflammatory drugs.

7

CANCER

"Hi Dr. Abodeely, my name is Linda Smith. My mother was recently diagnosed with cancer and I think she should use cannabis. Can you help us?"

"Given my diagnosis of cancer, would I benefit from cannabis therapy?"

Unfortunately, I am approached with these two questions all too frequently. In 2018, the country saw over 1.7 million new cancer diagnoses, and cancer was the reported cause of over 600,000 deaths.[62] Informing patients of a newly diagnosed cancer, operating on them, and supporting them throughout their treatment remains one of the most emotionally challenging aspects of my profession, and cannabis therapy has been a welcomed and beneficial tool when caring for these patients.

There are several reasons patients diagnosed with cancer may choose to consume cannabis. The most common of these is for the nausea and vomiting induced by chemotherapy, which is cited by 40% to 90% of patients undergoing this type of treatment, including those who already use antinausea medications as part of their treatment plans. The problem is overwhelming: one review from 2015 found that a third of cancer patients—who received a combination of 5-hydroxytryptamine 3 (5-HT3) antagonist and corticosteroid medications—were not able to overcome nausea and vomiting, despite a prophylaxis.[63] Unpleasant on their own, nausea and vomiting are also a frequent cause of dehydration, weight loss, reduced appetite, and overall diminished quality of life.

The cannabinoid system is highly involved in the regulation of nausea and vomiting. And while most conventional pharmaceuticals have a single mechanism of action, cannabis has the ability to combat nausea and vomiting at multiple levels—that is, both by attenuating the nausea response in the central nervous system, and by directly interacting with tissue in the gastrointestinal tract.

Numerous clinical studies have highlighted the efficacy of cannabis treatments in this area, particularly among patients who cannot tolerate oral

medications due to nausea, and who seek out cannabis in its inhalational form. As a result, the National Academy of Science, Engineering, and Medicine has made the conclusion that, "there is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment against chemotherapy-induced nausea and vomiting."[64]

Cannabis's role in the treatment of cancer is a classic example of the benefits of the Entourage Effect, which is discussed in Chapter 3. Up until 2014, if I was treating a patient for colorectal or bowel cancer, the only way I could engage the endocannabinoid system to address issues like severe nausea, anorexia, or weight loss would be by prescribing Marinol (nabilone), a pure, synthetic form of THC approved by the FDA in the 1980s. As later studies showed, Marinol never did as much to bring cancer sufferers relief as treatments involving a full cannabinoid and terpene profile—that is, by using products from whole cannabis, which could address the causes of nausea from multiple channels on the cellular level. We now know that THC reduces vomiting by binding to cannabinoid CB1 receptors, but that CBD, too, may have a role in reducing nausea, based on its interaction with serotonin receptors. Furthermore, several preclinical studies indicate that CBDA, the naturally-occurring acidic version of CBD, is a more potent antiemetic than CBD; because tinctures and certain edibles are often prepared without a great deal of heat or combustion, these products may provide an even more optimal response to vomiting.[65]

We can also see the Entourage Effect at work when cannabis is used for the neuropathic pain associated with chemotherapeutic agents and regimens. Many of these regimens can directly cause trauma to nerves, but they can also increase pain-sensitivity—that is, by activating the nerves involved in transmitting a pain signal to the brain; this side effect impacts between 35% to 75% of patients receiving chemotherapy. The discomfort may diminish their quality of life, and in many cases has moved cancer sufferers to delay or entirely abandon their therapy.

Right now, there is emerging literature supporting the use of cannabis for chemotherapy-induced neuropathic pain, based in part on what we know about the endocannabinoid system's role in reducing pain signals. Specifically, the phytocannabinoid CBD has been shown to inhibit the expression of fatty acid amide hydrolase (FAAH), an enzyme that typically breaks down the endocannabinoid AEA, a negative feedback mechanism that causes a nerve signal to slow down. This is just one of the ways that plant cannabinoids can interact with the receptors involved in nerve pain conduction, including the CB1 and CB2 receptors, serotonin and vanilloid receptors, orphan G-protein coupled

receptors (GPR55), and peroxisome proliferator-activated receptors (PPARs). (Table 1)

Table 1. Targets of cannabinoids which play a role in pain signaling.

- Cannabinoid receptor-1 (CB1)
- Cannabinoid receptor-2 (CB2)
- Vanilloid receptor (TRPV1)
- Serotonin receptor (5-HT1a)
- Orphan G-protein coupled receptor (GPR55)
- Peroxisome proliferator-activated receptors (PPARs)

For a more in-depth discussion of how plant cannabinoids can interact with the role cannabis can play in the treatment of pain, I'd encourage you to read Chapter 5. Cancer patients, specifically, may be interested in how cannabis can address nociceptive pain caused by metastasis—that is, by the direct pain of a tumor that invades nerve tissue, and by its compression of the nerve cells that carry a pain signal. Cannabis's ability to reduce these signals and alleviate nociceptive pain has been well established. Moreover, by using cannabis in the place of opioid medications for the treatment of pain, patients can avoid unpleasant side effects, including constipation, fatigue, somnolence, and sedation, as well as serious addiction and dependency risks—all of which, in turn, can affect the loved ones who are caring for a person with cancer. This can be especially important for terminally ill patients, and can allow for more meaningful interactions with the family and friends of someone managing end-of-life care.

Lastly, it's important to talk about cannabis's potential role as a chemotherapy agent. This is a controversial subject; on one hand, I think cannabis products—in particular those with high levels of CBD—offer a lot of potential value in direct chemotherapy, albeit based on studies involving pre-clinical trials, with animal models. On the other hand, there is some evidence that the activation of certain cannabinoid receptors can actually accelerate the growth of certain kinds of cancer. With this in mind, I have encouraged those considering using cannabis—whether as a chemotherapeutic agent or otherwise—to consult a medical cannabis specialist.

Obviously, it's important to make sure this approach will not do more harm than good. One review of the role of the ECS in cancer treatment found that CB1 receptor increased with the progression of lymphoma, chemically-induced hepatocarcinoma, and the growth of human epithelial ovarian tumors. Naturally, this was correlated with a worse prognosis, as were cases involving colon cancer,

pancreatic cancer, and prostate cancer. Another study saw increased levels of CB2 expression correlated with more severe cases of breast cancer, and still another found that CB2 receptor overexpression enhanced patients' predisposition to leukemia virus infection.[66]

This is just a partial list, and yet other reports have associated the endocannabinoid system with anti-cancer effects. Specifically, THC has been shown to bind to cannabinoid receptors that stimulate the synthesis of compounds called sphingolipids, and activate a signaling route in a cell's ectoplasm that leads to autophagy and cell death in some tumors.[67] Several experiments have shown this mechanism to have had an anti-tumorigenic role in cases of glioma and melanoma, as well as pancreatic and hepatic cancers. In other cases, cannabinoids have been shown to have a role in slowing or halting the rate of tumor growth, and in decreasing blood flow to cancer cells, as well as in removing the cloaking that allows cancer cells to elude the immune system.

On an anecdotal basis, I've found cannabis to show some significant promise when included as part of an individual cancer patient's treatment plan, but this is not enough support for any doctor to make a wholesale recommendation. For their part, the National Academies of Sciences, Engineering, and Medicine released a report in 2017 in which they ruled that there is, "insufficient evidence to support or refute the conclusion" that cannabinoids are an effective treatment for cancers, including glioma.[68] I fully expect cannabis therapy will be used in a targeted fashion in the future treatment of a variety of cancers.

Lastly, I should mention that in addition to its usefulness for nausea, vomiting, or pain, cannabis can also form part of an effective response to other ailments common to cancer, including depression and anxiety, as well as gastrointestinal issues associated with chemotherapy, such as diarrhea or irritable bowel syndrome. Readers interested in an explanation for how medical cannabis can help to address these issues should consult Chapters 8 and 9.

8

DEPRESS ION AND ANXIETY

It is currently estimated that over 300 million people worldwide suffer from depression.[69] Depression is an extremely widespread problem, and I believe nearly every one of us experiences it at some point in our lives. Any number of life's ordinary stressors can leave us feeling hopeless, vulnerable, lonely, or simply sad; if you've ever had to deal with the loss of a job, or had a cherished relationship go sour, then depression can be a normal, short-term reaction.

Clinical depression, however, is usually manifested by feelings that are much more frequent and severe, and are brought on without a known trigger. People who are clinically depressed can often have trouble concentrating or remembering important information, and find it difficult or effortful to complete normal, everyday tasks. In more severe cases, these can be paired with unexplained aches and pains, or frequent thoughts of death or suicide. Lack of appetite and difficulty sleeping are more common occurrences, as are a loss of interest in our work, or in the things we do for fun.[70] Furthermore, depression is regularly associated with feelings of restlessness, irritability, or dread—all of which are also reported by people suffering from anxiety.

Because the diagnosis and treatment of depression and anxiety often go hand in hand, I've decided to incorporate my discussions of the two ailments into the same chapter. If someone is anxious, it can cause them to be clinically depressed, and vice versa. Moreover, because the chemical pathways associated with anxiety and depression are closely correlated, several of the medications prescribed for depression or anxiety can be used to treat either disorder.

Clinical depression and anxiety are closely correlated with problems in the natural distribution of serotonin, a vital neurotransmitter, produced on demand by cells in our central nervous system. Serotonin plays an important role in regulating our mood, appetite, and sleep patterns, and, as it happens, treatments for depression and anxiety often involve the use of *selective serotonin reuptake inhibitors* (e.g. Prozac, Paxil, etc.), which can increase serotonin levels in the brain. Although these conventional pharmaceutical agents can be highly

effective, they are often associated with multiple side effects, including nausea, insomnia, constipation, dizziness, or abdominal pain. In some cases, they even have the potential to exacerbate depression symptoms, or lead to suicidal thoughts.

For people suffering from depression or anxiety, what's important to recognize is that the human endocannabinoid system has been shown to play a critical role in regulating release and reuptake of serotonin. Higher levels of natural endocannabinoids in our body have been associated with an antidepressant effect, in part because cannabinoid receptors—which are found throughout the central nervous system, and are crucial in maintaining our sense of wellbeing—are particularly abundant in cells whose sole purpose is to manufacture serotonin where it is needed. Endogenous cannabinoids and plant-based cannabinoids both have the power to increase the transmission of serotonin by acting as a serotonin receptor agonist—in essence, producing the same reaction in the synaptic cleft as serotonin itself.

Another mechanism of action by which cannabinoids may have an antidepressant effect is through their interaction with the hippocampus, a region of the brain involved in storing memory and regulating mood. During times of stress, the body produces steroids known as glucocorticoids, which can cause the hippocampus to atrophy and shrink, often resulting in diminished memory and depressed mood. Recent studies have demonstrated that cannabinoids can help combat this problem through *hippocampal neurogenesis* (regrowth and development in nerve tissue), which can be activated by the expression of cannabinoid type-1 receptors. Natural endocannabinoids and plant-based cannabinoids have both been shown to accelerate this process.

The role of the endocannabinoid system in regulating anxiety continues to be studied closely as well. Like certain chronic pain conditions, certain heightened emotional states can often be associated with the over-excitation of a given nerve signal. By limiting the release of certain neurotransmitters, cannabinoids can have a retrograde ability to attenuate those signals, taking part in a negative feedback loop, and consequently slowing those responses down.

You may ask yourself why exercise is so often recommended as a way to combat depression or anxiety. A frequent explanation is that exercise makes you feel like you're doing something healthy for your body, affirming your self-worth, and distracting you from stressful or worrisome thoughts. While all of this is valid, recent studies have demonstrated that exercise also increases our body's natural production of cannabinoid neuromodulators, such as AEA and 2-AG. "Runner's high"—a condition long believed to be the result of increased endorphins—may actually be caused by the release of endocannabinoids, which

can raise serotonin levels in the brain during a workout, leading to improvements in mood.

When considering whether plant-based cannabis might make an appropriate part of a healthy treatment for depression or anxiety, it's worth remembering that the research is mixed. To begin with, several studies have found increased rates of depression and anxiety with cannabis use, and anxiety and paranoia continue to be some of the most commonly reported adverse effects of cannabis use. Despite this, one study, published in 2006, the *Journal of Addictive Behaviors*, reported that individuals who used cannabis in moderation reported fewer instances of depressed mood, a more positive effect, compared to non-cannabis users.[71] Four random-controlled trials found that the cannabis extract nabiximols —as well as the synthetic cannabinoids dronabinol and nabilone—reported an improvement in subjective symptoms of anxiety.[72]

In another random-controlled trial, subjects receiving a 600 milligram CBD supplement also reported less subjective anxiety symptoms during public speaking than those who'd taken a placebo.[73] CBD was also associated with significantly reduced activity in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and increased activity in the right posterior cingulate gyrus, indicating that CBD reduced symptoms in people with social anxiety disorder, and that this was related to its effects on the limbic and paralimbic areas of the brain.[74] In view of this evidence, a report by the National Academies of Sciences, Engineering, and Medicine concluded that there is, "limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders."[75]

The variations in response to cannabis have been hard to explain. In conversations with my own patients, I have found that while THC is frequently associated with anxiety and paranoia—particularly at higher doses—patients taking cannabis products that contain no THC, for their part, have reported higher levels of depression. From what we can tell, certain cannabinoid receptors in the brain, including those responsible for emotional and behavioral health, can increase anxiety when they are activated, while others can help to reduce it. In short, cannabis is one substance for which there appears to be a *biphasic* (or "bell-shaped") dose response: lower doses of THC may help alleviate anxiety, while higher doses will increase these symptoms, and before we can fully comment and recommend cannabinoids for depression, there remains a large knowledge gap that must be closed. Having said that, on an anecdotal level, many of my patients and consumers of cannabis report improvement in their

symptoms of depression and anxiety.

While I do believe that there is a role for the use of cannabinoids to treat these disorders, it's obvious that this must be done with caution, and if you're considering cannabis as part of a treatment plan for depression and anxiety, I would make several recommendations. Firstly, I would recommend starting at *very* low doses, and titrating slowly over the course of several weeks. This is a simple way to reduce risks or adverse effects; even if you've sought out the best advice, and taken your time in choosing the right cannabis product, there is no way to be completely sure of how your body will respond. Second, I would try to find a product with a low THC content, especially if you are suffering from anxiety, or are predisposed to it. The reason for this is to reduce the probable activation of CB1 receptors, which has been associated with increased anxiety levels at higher doses. (A more comprehensive discussion of dosage levels and their implications can be found in Chapter 16.)

Next, I would suggest you start by consuming cannabis by inhalation—preferably with the use of a vaporizer. This allows you to feel the effects of cannabis relatively quickly, making is easy to titrate slowly; in the event that you begin to feel more anxious, the effects will also wear off faster than other routes of administration. It's worth bearing in mind that oral consumption of cannabis is subject to the first-pass metabolism, and that its active ingredients will be processed by the liver, which is responsible for detoxifying substances we ingest through our intestinal tract. This will cause some of the compounds found in cannabis to be altered in ways which may have unwanted effects: a certain amount of THC, for example, will be converted into 11-OH THC, a much smaller molecule, that passes much more easily through the bloodbrain barrier. 11-OH THC also has much higher affinity for the CB1 receptor, and can overstimulate the areas of the brain responsible for our mood, leading to increased levels of stress and anxiety. For these reasons, anyone considering cannabis for anxiety should avoid edibles at first, since these can have a delayed and sometimes inconsistent onset of action.

9

GASTROINTESTINAL CONDITIONS

As a surgeon who specializes in gastrointestinal conditions—ranging from intestinal cancers to inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis—I've had a great deal of experience incorporating cannabis into my patients' treatment plans. In addition to inflammatory bowel disease and colorectal cancer, patients have frequently inquired about the use of cannabis for conditions including irritable bowel syndrome, liver disease secondary to cirrhosis, gastroesophageal reflux disease (GERD), chronic abdominal pain, and metabolic conditions, including obesity.

Part of the reason cannabinoid therapies have been so effective in addressing diseases of the small bowel, colon, and rectum is because the endocannabinoid system plays an extremely important role in the gastrointestinal tract. Enteric nerves in the intestines, which are responsible for motility and enzyme production, are abundant in CB1 receptors, while immune cells in the digestive tract, which form our first defenses against viruses and bacteria entering the body, express a number of CB2 receptors. Cells in the stomach and intestinal tissue express most other cannabinoid receptors as well, including GPR 55, transient receptor potential cation channel subfamily V member (TRPV), and peroxisome proliferatoractivated receptors (PPARs), which together help to maintain a healthy mucosal epithelial barrier against pathogens, altering gastric acid and intestinal secretions, regulating appetite, and surveilling the growth of potential cancers.

Irritable Bowel Syndrome

Irritable bowel syndrome is a disorder characterized by abdominal pain, discomfort, bloating, and altered bowel habits, and is estimated to effect approximately 20% of adults worldwide. There are three main categories of irritable bowel syndrome, including diarrhea-predominant (IBSD), constipation-

predominant (IBS-C), and mixed-pattern irritable bowel syndrome (IBS-M). The pathophysiology of IBS is thought to be multifactorial, and may include a psychosocial component as well.

Patients with IBS-D frequently experience abdominal pain, diarrhea, and bowel urgency, often brought on by stress or a meal, but sometimes appearing without a visible trigger. The endocannabinoid system can have a role in managing these symptoms through multiple channels: activation of CB1 receptors, for example, has been shown to inhibit muscle contractions and reduce intestinal motility, while activation of CB2 receptors promotes the immune cells in the intestine, and can help to enhance its mucosal barrier, and reduce the amount of inflammation within the intestinal lining.

In addition to numerous patient surveys, preclinical data, and anecdotal data support its benefits, there have also been limited randomized controlled trials looking at cannabis for irritable bowel syndrome. One randomized study looked at 52 patients; compared to those who received a placebo, subjects who received cannabinoid therapy were found to have a significantly fewer colonic contractions during fasting states, and reported a significant reduction in bowel contractions and motility.[76] More research is required before we can make definitive recommendations on optimal dosing for patients suffering with irritable bowel syndrome, but the outlook for these treatments looks promising.

Inflammatory Bowel Disease

Inflammatory bowel disease is a condition characterized by an abnormal immune response within our gastrointestinal tract. Although the mechanisms are still not entirely understood, we do know that patients with IBD have a genetic predisposition to mounting an uncontrolled immune response to the bacteria within our gastrointestinal tract, and sometimes as a result of other environmental factors. Since IBD is an autoimmune condition, involved with inflammation, it should be no surprise that the endocannabinoid system is an ideal target to help combat this illness. It’s also worth mentioning that many of the conventional pharmaceutical agents used to treat IBD are often associated with significant side effects and toxicity; they have the potential to make patients more susceptible to other opportunistic infections and even cancer.

Cannabinoid therapy is used to treat a variety of symptoms associated with IBD, but also to treat the disease itself. In my clinical practice, the majority of my IBD patients report significant improvements with regards to abdominal pain, diarrhea, and overall quality of life. This is in correlation with the other

published surveys, anecdotal data, and some smaller prospective studies, which report similar successful outcomes. There have also been experimental models showing decreased intestinal inflammation, motility, nausea, and diarrhea with the use of cannabis for patients with IBD: animal models, for example, have shown decreased intestinal inflammation with the introduction of phytocannabinoids like THC, CBD, and CBG, or with synthetic compounds such as O-1602 (an analog of CBD), and WIN-55,212-2; a nonselective cannabinoid receptor agonist.[77]

Colorectal Cancer

Given my background as a surgeon, I felt it necessary to expand a bit on the use of cannabis therapy for patients who are being treated for colorectal cancer (CRC). Each year, about 150,000 people are diagnosed with this type of cancer, and approximately 50,000 die from it. Unfortunately, only about half of Americans over the age of 50 are known to regularly avail themselves to preventive screenings for CRC, which are often lifesaving. This may be why CRC is currently the fourth most common form of cancer—behind cancers of the breast, lung, and prostate.[78]

Treatment options for CRC typically include surgery, chemotherapy, and occasionally radiation. These interventions can be highly disruptive in themselves, and I would encourage readers to have a quick look at Chapter 7, which discusses how cannabis can help to reduce the need or alleviate the burdens associated with them. The chapter goes into some detail on how cancer patients—including those diagnosed with CRC—can use cannabis to relieve some of the pain related to cancer, reduce chemotherapy-induced nausea and vomiting, and even use cannabis as a direct chemotherapy agent. The positive outcomes of cannabis use for pain and chemotherapy-induced nausea and vomiting are well established. Moreover, the data describing its use as a chemotherapy agent for colorectal cancer, while not as conclusive, is still definitely worth taking into account.

Preclinical studies have attributed numerous possible anticancer effects to the work of cannabinoids. Over the years, the endocannabinoid system has indicated some ability to detect abnormal tumor cells, destroy these cells (apoptosis), inhibit blood flow to tumors, and inhibit the ability of these tumors to migrate and spread. Despite this, it’s worth remembering that cannabinoid therapy for CRC is extremely complex, and that caution must be used when recommending

cannabis for CRC, since certain cannabinoid receptors, when activated, may in fact promote tumor growth and progression. Cannabinoid receptors such as CB1 and GPR55, for example, have been shown to induce tumor growth and metastasis in animal models.

On the other hand, activation of the CB2 receptor has been associated with tumor suppression. Although the mechanism by which activation of CB1 and GPR55 may be detrimental to patients with CRC is not understood, we can infer that activation of CB2 is involved in assisting our immune system to identify and destroy certain tumor cells before they develop into malignancies. Again, with this in mind, I would urge patients who are diagnosed with CRC and are considering cannabinoid therapy to consult a provider who specializes in cannabis, to help make the right recommendations.

10

SLEEP DISORDERS

Some of the oldest applications of medical cannabis has been for insomnia and other sleep disorders. Pharmacists have seen the potential for cannabis to affect our sense of wakefulness or relaxation for millennia. The mechanisms behind this have only been established in the past few decades, as research has accelerated, and more people have looked for a treatment for ailments like insomnia, while hoping to avoid over-the-counter sleeping pills or more powerful hypnotics.

The demand for these interventions is dismaying. According to data from the American Academy of Sleep Medicine, 33% of adults and 20% to 40% of children and teenagers experience some form of mild insomnia. If this sounds insubstantial, it's worth remembering that the seemingly-passive act of sleeping is a vital and extraordinarily dynamic process—as important as eating or drinking—during which the body detoxifies and repairs tissues, regulates appetite and blood pressure, and helps the brain recover and process information.[79] People who go without sufficient sleep are at greater risk of infectious disease, diabetes, and obesity, and have reduced physical coordination and endurance, in addition to impaired judgment and cognition. As you can imagine, this makes our workplaces less productive, our social lives less rewarding, and our roads less safe. Taken as a whole, it's been estimated that the nationwide problems attributable to insomnia represent a $90 billion burden to the U.S. economy each year.[80]

Nearly every organ system that benefits from sleep is rich in endocannabinoid activity, including cells that govern immunity, metabolism, digestion, and brain function. Cannabinoid neuromodulator levels in the nervous system fluctuate inversely over a 24-hour sleep cycle—2-AG is at higher levels during the day, while AEA is more abundant at night—and both compounds are known to dock with CB1 receptors on brain cells responsible for governing rest and wakefulness.

All of this offers a great deal of promise for cannabis as a potential treatment

for sleep disorders, but studying the role of the cannabinoid system on sleep regulation is a tricky undertaking. For one thing, research has shown that even isolated compounds from cannabis, including THC and CBD, have shown a *biphasic* (or "bell-shaped") effect on wakefulness or alertness, meaning patients can often have inverse responses to cannabis on their sleep cycles, depending on the dosage level. A study from 1981, for example, found that subjects who received 160 milligrams of CBD per day, over a period of several weeks, reported significantly longer sleep times than the control group, which would be encouraging news for anyone considering cannabis as a treatment for insomnia.[81] On the other hand, a study from 2014 found that rats were more wakeful during the "lights on" period after receiving small injections of CBD—about 10 micrograms per 5 microliters—into either the cerebrospinal fluid or the hypothalamus.[82] This would support the use of CBD as a potential treatment for narcolepsy, or drowsiness during the day.

Another complication for researchers has been the fact that these disorders often coexist with a number of other ailments. For example, it's not unusual for chronic pain sufferers or people with irritable bowel syndrome to also report difficulty getting regular, restful sleep. How cannabis can be used to address these ailments can be addressed individually and is discussed in Chapters 5 and 9, but one insightful review from 2007 examined the usefulness of medical cannabis in treating the disruptions to sleep caused by other conditions.[83] After looking at papers for which 2,000 subjects took an oral-mucosal spray containing THC, CBD, or an equal combination of the two, the authors found significant improvement in sleep quality among people with multiple sclerosis, peripheral neuropathic pain, intractable cancer pain, and rheumatoid arthritis. Reports of side effects or substance dependence were minimal, and 40% to 50% of the subjects involved reported good or very good sleep quality.[84]

In sum, the review examined thirteen studies, for which seven reported significant relief of sleep disorders in their subjects, while the greatest amount of improvement was shown among patients taking oral-mucosal sprays with a combination of CBD and THC (15 milligrams each). Considering the potentially sedative properties of terpenes like terpinolene, nerolidol, phytol, linalool, and myrcene, this finding lends further support to the reliability of the Entourage Effect, and the idea that cannabis with a full cannabinoid profile can be more useful than any single compound taken on its own.

Post Traumatic Stress Disorder

Another ailment that often coexists with sleep disorders is Post Traumatic Stress Disorder (PTSD), which is an increasingly common target of cannabis therapy in states where medical cannabis has been legalized. The support for this is substantial: one study from 2014 examined 170 patients who visited a dispensary in San Francisco, California, and out of this group, patients who had been diagnosed with PTSD reported that they were more likely to use cannabis to improve the ability to fall or stay asleep, and that this was, in fact, the primary motivator for their use.[85]

Some of us may read these results as an indication that people with PTSD were merely pursuing cannabis as part of an attempt to self-medicate. I think this is a mistake, and that by describing cannabis as one unhealthy coping mechanism among many, we overlook a great deal about the nature of the disorder.

PTSD, after all, is not a single-pronged condition. While difficulty sleeping may be a prominent symptom, it is also associated with states of prolonged anxiety—a separate ailment, for which cannabis can often be a helpful and appropriate treatment. (See Chapter 8 for a discussion on cannabis and anxiety.) Part of this is supported by a 2013 study of people suffering PTSD, which found the subjects with the condition had much lower levels of AEA, an endocannabinoid that binds to brain cells that regulate mood.[86]

There is also evidence that cannabis can reduce the duration of the Rapid Eye Movement (REM) stage, a segment of the sleep cycle when PTSD sufferers frequently experience nightmares. One study, from 2009, examined 47 patients who had had recurring nightmares related to PTSD, which persisted over the previous two years, despite the use of antidepressants and regular visits to a psychiatrist. After taking the THC isolate nabilone in doses ranging between 0.2 and 4.0 milligrams each night, 72% of the subjects reported either a severe decline in nightmares, or stopped having them entirely.[87] Notwithstanding the serious substance abuse problems disproportionately shouldered by people who have experienced severe emotional trauma, I think we should resist the temptation to characterize cannabis as a just another sign of distress, rather than a medicine with considerable benefits; if used under the supervision of a qualified specialist, it can have a place in the healthy treatment of sleep disruptions caused by PTSD.

11

MIGRAINES

Migraine headaches are yet another ailment for which cannabis has been prescribed for literally centuries, even though the finer details of this interaction remain underexplored. Use of cannabis in India, which dates back to at least the third century BCE, was supported by Ayurvedic treatments for headache-like conditions including migraines.[88] The plant was probably used for the treatment of headaches in Ancient Assyria, and by Sabur ibn Sahl, a ninth century Persian Christian physician, whose texts had a lasting impact on pharmacopeia of the medieval Arab world.[89] Migraines were also one of the last medical applications of cannabis to be approved by aboveboard doctors in the United States after the passage of the prohibitive Marijuana Tax Act of 1937. In 1942—a year after cannabis was removed from the official U.S. Pharmacopoeia—the editor of the Journal of the American Medical Association endorsed oral cannabis treatments for migraines brought on during menstruation.[90]

Cannabis continues to be a reliable treatment for migraine headaches in the present day, when it remains the sixth most disabling illness in the world, and when four million people in the U.S. suffer from fifteen or more migraine headaches per month.[91] These may begin with sensory or emotional triggers, such as hunger, anxiety, or certain smells or tastes, and mild warning signs might include dizziness, or an increased sensitivity to light; for many people, these symptoms can intensify into blurred vision, severe nausea, and debilitating pain.

Conventional approaches to migraine headaches each have their drawbacks. As with other forms of pain, some over-thecounter pain relievers such as ibuprofen and acetaminophen are sometimes helpful, but their effect can be fairly mild. Some patients have allergic reactions to these drugs, and they have been associated with liver or gastrointestinal damage when taken regularly over long periods of time. Triptans such as zolmitriptan and naratriptan are a more popular approach, given their ability to dock with serotonin receptors on blood vessels and nerve endings, thereby blocking the release of inflammation agents in the brain. They’re likely to bring some level of relief, but triptans are also

fairly expensive, so much so that insurance companies may restrict coverage on the medications past a certain amount. Also, the side effects are considerable, and include dizziness, uncomfortable warmth, nausea, and tightness in the chest, as well as “rebound” headaches.

Consequences like these can sometimes be worse than the ailment itself, which may be why the demand is growing for cannabis-based headache treatments whose side effects are negligible. It helps that cannabinoids have a role in managing many of the physiological dysfunctions associated with migraines, and there’s some speculation that these symptoms intensify among migraine sufferers because of an “endocannabinoid deficiency”—that is, a defect in the effective channels that would balance and attenuate symptoms like pain, inflammation, and nausea. For example, one study from 1996 found that the injections of THC bound to cells in the periaqueductal region of the brain, which is responsible for some of the pain and compression associated with headaches.[92] A more recent study, from 2010, found that CB1 receptors were abundant among brain cells involved in the transmission of migraine-related pain, including the sensory terminals, and the dorsal root ganglia.[93]

All of this is consistent with the results of a study from 2016, involving 121 subjects who had been prescribed medical marijuana from one of two clinics in Colorado. Of these, 48 patients reported fewer and less frequent migraine headaches, and as a whole, the group reported a diminution from 10.4 to 4.6 headaches a month, on average. Fourteen patients reported unwanted side effects or problems with dosing; this was more prominent among those taking edibles than those taking cannabis by inhalation.[94] One of the more recent reviews of the efficacy of cannabinoids in addressing migraines was published in 2018, in *Frontiers in Pharmacology*, echoed the speculation that migraines sufferers may possess lower than normal levels of CB1 and CB2 receptors in the brain—particularly among meningeal trigeminal nerves and vessels, and among dural mast cells.[95] In outlining the *Clinical Endocannabinoid Deficiency* (CEDC) hypothesis, the authors draw a direct line between the availability of endocannabinoids and “numerous mental state disturbances and, particularly, to migraine.”

This subject offers a tremendous amount of hope for chronic migraine sufferers, and a field of investigation for clinicians. In the years to come, conditions associated with migraine headaches will foster an even greater demand for research into the anti-convulsive, antiemetic, anti-inflammatory, and pain-relieving benefits of medical cannabis.

12

SKIN DISORDERS

In 2018, a market research firm based in Delaware valued that the market segment for topical cannabis products was $349.1 million in the previous year, and predicted a compound added growth rate of 37.4% by 2024.[96] Patients with skin problems may represent a sizeable market for producers of medical cannabis products, in part due to the growing research into creams, ointments, and patches that can potentially treat inflammation and immune disorders, which are in particularly high demand among aging sections of the population.

The evidence for the efficacy of these approaches has been around for a long time. In the first textbook of dermatologic therapeutics, published in 1881, Dr. Henry Granger Piffard wrote that, “a pill of cannabis indica at bedtime has at my hands sometimes afforded relief to the intolerable itching of eczema.”[97] But as with other cannabis treatments, there’s still a lot to be explored about the potential for topical cannabis for itchy or inflamed skin, or for reducing the incidence of microbial infection.

What we do know is that the skin is rich in cannabinoid receptors, which have a direct role in the regulation of histamines and other hormones that transmit signals of irritation or pain. This was borne out by a 2010 study from Italy, which connected a high level of anti-inflammatory activity to small applications of Croton oil containing cannabinoids on mice that had been affected by dermatitis. Cannabinoids outperformed comparable doses of the nonsteroidal anti-inflammatory drug (NSAID) indomethacin, and the considerable success of this intervention was attributed to activation of CB2 receptors in the skin by THC, but the authors were also convinced of the efficacy of CBD on other, more obscure cannabinoid receptors—including vanilloid receptor TRPV1, cyclooxygenase-2, and inducible nitric oxide synthase.[98] Another study, from 2016, found that CB1 receptors, when activated, could inhibit the release of histamines and some inflammatory mediators, which are associated with pain and itching of the skin.[99] This was supported by yet another study, from 2015, which supported the possibility of cannabinoids in addressing

atopic dermatitis, a chronic disease for which itching and inflammation are the primary symptoms.[100]

One particularly interesting study examined the relationship between skin inflammation and difficulty sleeping: In this trial, subjects were asked to describe both severity of itch and loss of sleep after using a cream containing n-acylethanolamine family, which is thought to attenuate inflammation through the cannabinoid receptors. After six days of use, 60% of the subjects indicated an improvement in symptoms.[101] In yet another study, from 2007, researchers looked at the ability of plant-based cannabinoids to inhibit the proliferation of a hyper-proliferating human keratinocyte cells, whose accumulation is one of the key markers for psoriasis. The subjects showed significant reductions in keratinocyte proliferation after 72 hours of exposure to THC, CBD, CBN, and CBG, which the authors attribute to the activation of PPAR-g or GPR-55 receptors, rather than CB1 or CB2.[102] In June 2018, researchers from the National Eczema Association declared that cannabinoids, "possess anti-inflammatory, antimicrobial and anti-itch qualities."[103]

Another area in which topical cannabis treatments show a great deal of potential is in the treatment of bacteria-related skin disorders. One study from 1976 indicated that isolates of THC and CBD were effective in reducing samples of staphylococci and streptococci, two bacteria associated with acne.[104] Another study, from 2008, found that the plantbased CBD, CBC, CBG, THC, and CBN were substantially potent against a variety of *Staphylococcus aureus* strains, which were resistant to the antibiotic methicillin (MRSA).[105]

All of this is encouraging news for people with minor to severe skin ailments. Having said that, I also have some words of advice for eczema and dermatitis patients who are considering giving topical treatments a try. To begin with, it's worth paying special attention to the list of ingredients, since many products on the market contain terpenes or fragrances that can be harmful or irritating. Excess solvents that have been added during manufacturing process could also be present, and these are likely to dilute the therapeutic effects of the cream or ointment. It's also worth remembering that because the active ingredients in cannabis are lipophilic, it's difficult for these compounds to penetrate the aqueous barriers of the skin into deeper tissue, despite promising patient and consumer feedback.

Today, there is very little oversight for determining the safety or potency of cannabis-based skin treatments, and so it's difficult to make any judgement about a product's consistency, or the presence of contaminants, including pesticides from the extraction process, and additives such as heavy metals. Until

more clinical data is available for specific cannabis skin products, it’s best to seek out items that have been tested by a third party (instead of by the manufacturers themselves), and to pay attention to which state markets have their own regulatory testing and consumer protection safeguards in place.

13

METABOLIC DISORDERS AND DIABETES

Among the most misunderstood aspects of medical cannabis is its role in managing appetite and metabolism. Given the frequency with which cannabis treatments have been prescribed to patients with cancer, AIDS, or HIV suffering from severe tissue atrophy and decreased hunger—and the well-known tendency for cannabis to stimulate appetite, or enhance the taste and smell of certain foods—many people erroneously believe that plant cannabinoids uniformly cause people to eat more and gain weight. The relationship between the endocannabinoid system and the body's management of appetite or energy storage are significantly more complicated than this, and cannabis actually has a rich potential for treating obesity and blood sugar disorders, including diabetes.

This is borne out, firstly, by the epidemiological evidence, in which cannabis use has been inversely correlated with metabolic dysfunction and weight gain. One study from 2010 compared incidents of diabetes and cannabis use in the United Kingdom, and found that reported diagnoses of diabetes had increased between 2003 and 2006, at the same time that cannabis use in England had declined.[106] In the United States, in states where medical cannabis is still restricted, diabetes remains a growing health problem. Nationwide, the disease affected 30.3 million Americans—nearly a tenth of the population—in 2015.[107]

Moreover, research has indicated that there are multiple channels by which cannabinoids may have the potential to ameliorate the dysfunction of insulin and blood sugar management that are associated with diabetes. Much of this has to do with the potential for cannabinoids to increase the release of insulin by β-cells, which are found in the pancreas. A study from 2006 found that activating the CB1 receptors expressed on β-cells from rats made them secrete higher levels of insulin; similarly, a study from 2007 found that THC could stimulate the release of insulin in rat pancreases by increasing the activity of lipoxygenase—an enzyme involved in lipid metabolism.[108] [109] At the same time, there is also reason to believe that cannabinoids may enhance cellular glucose uptake. This is supported by a 2009 study, which found that cannabinoids accelerated the

translocation of GLUT4, a transporter protein responsible for carrying glucose into fat and muscle cells.[110]

Within the nuclei of these cells, other cannabinoid receptors may have a role. There is a great deal of evidence, for example, of the role played by PPARS (peroxisome proliferator-activated receptors) to regulate insulin sensitivity and lipid metabolism, and a 2007 study found that activating these receptors improved metabolic abnormalities in blood sugar, insulin levels, and blood cholesterol in type-2 diabetic mice.[111] [112] With this effect in mind, doctors have prescribed thiazolidinediones (TZDs) to patients with diabetes in the past. However, there is reason to believe that a plant-based cannabinoids, which have a weaker affinity for PPARs, may therefore lead to fewer of the side effects associated with TZDs, including weight gain and heightened blood lipid levels.

What's particularly interesting is that certain cannabinoid receptors can actually reverse the problems associated with diabetes when they've been blocked. This is what led to the brief popularity of rimonabant, a compound which binds to CB1 receptors in the brain in such a way as to prevent other neuromodulators from activating them. The effects of rimonabant was investigated in a 2008 study, in which the authors treated 1,507 obese but non-diabetic patients with a supplementary dose of the compound, and found it significantly reduced their insulin resistance and helped with weight loss. Based on this logic, rimonabant was actually available as a weight-loss aid in Europe for a brief period of time, though many patients complained of adverse effects on mood, and it was withdrawn from the market in 2009.[113]

In the present day, what we know about CB1 receptors is still useful for those of us who are considering using cannabis to control as well as stimulate hunger. A lesserknown cannabinoid, THCV, has actually shown a great deal of promise for weight loss as an appetite suppressant, and its properties are worthy of further research. One study, from 2009, assessed the feeding behavior of fasting and nonfasting mice after treating them with THCV, positing that the compound could block the activation of CB1 receptors. The authors found that doses as small as 10 milligrams per kilogram of body weight suppressed food intake and inhibited weight gain for a period of six to eight hours, and that these effects continued when the mice continued to receive injections over four consecutive days.

Remarkably, no abnormal feeding patterns were observed after the mice stopped being treated. Though a separate series of interventions involving full-profile cannabis extract failed to produce the same result—probably due to the presence of THC—the effect of THC on appetite appeared to be surmounted

when the extract included a co-administration of CBD.[114] Together, what these trials seem to indicate is that despite the power wielded by THC, cannabis does not necessarily make you gain weight. It's an important insight, and by mentioning it, I hope to displace some of the stigma attached to cannabinoids and their connection to binge eating.

Patients who are considering medical cannabis with diabetes should be also aware of some of the collateral symptoms of this disorder, which cannabis can also help address. Probably the most prominent of these symptoms is hyperglycemia-induced neuropathic pain, which is brought on by oxidative stress on the nerve endings. For a study published in 2010, researchers looked at a sample of diabetic rats, and administered daily doses of *Cannabis sativa* ranging from 25 to 100 milligrams per kilogram of body weight. After fourteen days, the rats exhibited significant reductions in tingling, heat, and pain in the extremities associated with advanced diabetes.[115] Another study, from 2015, compared descriptions of spontaneous pain among sixteen patients with painful diabetic peripheral neuropathy, in a randomized, double-blinded setting. The participants were exposed to four single dosing sessions of placebo or cannabis, whose THC content ranged from low to high (1% to 7%), and reported a significant reduction in pain intensity that varied directly with the size of their dose.[116]

Of particular note are the signs that cannabis can be used to address some of the secondary consequences of diabetes, such as inflammation and pain, which are often classified as autoimmune symptoms. (For a more in-depth discussion of pain and inflammation, see Chapters 5 and 6.) Part of this is supported by a 2008 study, in which doses of CBD were administered to non-obese diabetic prone mice. After this intervention, subjects that had received this intervention showed less pancreatic damage than the control group, as well as a significant decrease in the presence of cytokines such as interleukin-12, a chemical signaling agent associated with inflammation, and an increase in the anti-inflammatory compound interleukin-10.[117]

Though the overall potential for cannabis in addressing metabolic disorders is not quite clear, there are some very encouraging signs, and I am convinced that cannabis treatments hold a great deal of promise in helping patients better manage problems related to blood sugar, pancreatic cell function, and insulin sensitivity. In the future, there is ample reason to believe that cannabis can have a positive role in treating these ailments.

14

NEURODEGENERATIVE DISORDERS

Given the progressive nature of many neurological diseases, whose consequences often worsen as people get older, it's commonly believed that these conditions only affect the elderly and middle-aged. This is a misconception. Brain injuries are actually the leading cause of death in individuals under 45, and multiple sclerosis (MS) affects men and women from a remarkably wide range of ages.

Neurodegenerative ailments such as traumatic brain injuries (TBI), MS, Alzheimer's disease, and Parkinson's disease represent a formidable challenge for the medical community, and cannabis absolutely has a role to play in treating them. Central nerve tissue that has been traumatized and degraded often has a higher rate of expression for cannabinoid signaling compounds, including vanilloid, adenosine, and 5-hydroxytryptamine receptors, and an abundance of research has indicated that the endocannabinoid system might be involved in the crucial mechanisms for restoring homeostasis in nerve cells affected by toxicity or inflammation.

How these mechanisms can be enhanced or repaired by plant-based cannabinoid therapy is an exciting new frontier. It may be complex—involving cannabinoids that activate receptors such as CB1 or CB2 in the brain, or the work of other neurotransmitters, such as c-aminobutyric acid, glutamate, opioids, peptides—but there is already a great deal of evidence that compounds such as THC or CBD have antiinflammatory, anticonvulsant, anti-oxidant, and anxiolytic properties. This makes medical cannabis a strong candidate for addressing neuroinflammation or oxidative injury brought on by trauma, and so a great deal of research has gone into how these compounds can help in the treatment of various neurodegenerative disorders.

Traumatic Brain Injuries

Newly-acquired knowledge of traumatic brain injuries and their long-term effects has led our country to a moment of reckoning. While these events were sometimes thought to be a minor or overstated issue affecting participants in football or other collision sports, documentaries and news reports over the last few years have uncovered an alarming amount of evidence indicating that even mild concussions can have serious, long-term consequences of the brain's internal chemistry. And while some segments of the population have been changing their behavior in light of these revelations—for example, participation in high school football has declined over the past three years, while flag football participation among six to twelve year olds has gone up by 38.9%—many adults and young athletes have continued to accept the risk.[118] In 2013, the Centers for Disease Control cited TBI in about
2.8 million emergency department visits, hospitalizations, and fatalities.[119]

The endocannabinoid system is intimately involved with the brain's potential recovery from these types of events. This begins in the moments following a trauma, when one of the first things that happens is the activation of NMDA receptors on immune cells in the brain, along with the release of glutamate, a neurotransmitter associated with inflammation. Excess levels of glutamate can cause an imbalance of sodium, potassium, and calcium ions in the synaptic cleft, and is a frequent cause of neural excitotoxicity, as well as dangerous levels of swelling and local compression. Cannabinoid modulators have a crucial role in correcting this imbalance: one paper from 2001 indicated that 2-AG could limit excitotoxicity by activating CB1 receptors on presynaptic nerve terminals to inhibit the release of glutamate.[120] A separate study has established that this process could take place in the cultured neurons from the brains of rats.[121]

This protective feedback effect of cannabinoids could also be seen on the formation of reactive oxygen species and other inflammatory agents, including and tumor necrosis factor-a (TNF-a). This was demonstrated in a 2000 study of immune cells in living mice, while another study, also from 2000, found that AEA could protect cortical neurons from rats that had been deprived of glucose and oxygen due to reduced circulation, an early and frequent occurrence following brain trauma.[122] [123] Still, another study, from 2006, found that 2-AG could also inhibit the release of cytokines including interleukin-1b and interleukin-6 in the brains of mice, which can be a cause of excess inflammation.[124]

Beyond these laboratory results, plant-based cannabinoids have shown tremendous promise in protecting nerve tissue from the disruptions to circulation caused by trauma. A study from 1999 traced this mechanism with the synthetic

cannabinoid WIN-55 212, which protected rat brains from the effects of reduced blood flow.[125] A more recent study, from 2014, found that out of 446 cases of traumatic brain injury, mortality rates were significantly lower among patients who tested positive for THC.[126] Another investigation, from 2016, indicated that stand-alone CBD isolates are particularly promising for protecting nerve tissue from being deprived of oxygen or glucose, by activating 5-HT1A serotonin receptors and the PPAR-gamma nuclear receptors in brain cells.[127]

Although there have been no federally-sanctioned clinical trials on the efficacy of whole plant cannabis in TBI, remedies containing CBD or THC show a great deal of promise for addressing the fallout of these events.

Multiple sclerosis

An even stronger case can be made for a cannabinoidbased intervention in cases of multiple sclerosis (MS), an autoimmune disease, which causes the lipid-based myelin sheaths that surround nerve channels to degrade. Over time, this tissue will be slower and less consistent in carrying signals, and later-stage symptoms might include tremors, spasms, chronic pain, incontinence, muscle spasticity, and severe reductions in coordination and mobility. Physicians are not required to report new cases of MS, and so the prevalence of the disease is difficult to measure, but most conservative estimates place the nationwide incidence between 250,000 and 350,000 people.[128]

The evidence for the endocannabinoid system's role in addressing MS is supported by a study conducted in 2007, in which researchers measured the levels of endocannabinoids in the cerebrospinal fluid of 51 people, 26 of whom had been diagnosed with the disease. Though 2-AG levels remained about the same between both groups, patients with MS showed six times the levels of AEA seen in the control group. Furthermore, the relapsing group also had heightened levels of AEA in their immune cells, indicating that this compound may play a crucial part in regulating the inflammatory response associated with MS.[129]

Clinicians have been using cannabinoids for treating MS symptoms since at least the 1990s, when patients in the United Kingdom began accessing nabiximols, a purified cannabis extract, for spasticity, neuropathic pain, and bladder dysfunction. In 2003, a survey by the Canadian Journal of Neurological Sciences found that 96% of MS patients were using cannabis, saying it helped with symptoms of muscle spasticity and depression.[130] In 2017, a survey of 595 participants, hosted by the Michael J. Fox Foundation and the National Multiple

Sclerosis Society, found that 59% of respondents had reduced prescription medication after beginning cannabis use, citing significant improvements in mood, memory, and fatigue.[131]

There is no known cure for MS, but cannabis clearly offers opportunities for symptomatic relief. If you're curious about how cannabis can be used to treat collateral issues such as pain or inflammation, a longer discussion can be found in Chapters 5 and 6.

Parkinson's disease

Multiple sclerosis is not the only condition associated with neurodegeneration and excitotoxicity that cannabis has some potential in treating. Though the cause of Parkinson's disease is unknown, doctors believe its root cause lies in the aberrant release of dopamine in the substantia nigra, a region of the brain within the basal ganglia, which governs movement and gait. This tissue is rich in cannabinoid receptors, and by activating them, it may be possible to reverse the frequent tremors, movement difficulty, and balance problems brought on by this disease. Cannabis therapies may therefore offer hope for the 10 million people who are living with Parkinson's worldwide.[132]

Much of this is believed to involve the complex interaction between the two principal cannabinoid modulators (AEA and 2-AG) and dopamine receptors in the basal ganglia. Some researchers have posited that cannabinoids may help improve the motor and non-motor symptoms of Parkinson's, based on the notion that excess dopamine activation can strengthen the connections between neurons in the cortex and striatum, while also leading to higher levels of neural excitability, so that some signals are carried at an uncontrolled or alarming rate. The basic theory is that AEA or 2-AG may have a role in slowing these signals down, or making them more even and consistent.

In support of these ideas, a small study from 2001 found that patients with motor problems related to Parkinson's saw significant improvement after taking doses of the synthetic cannabinoid nabilone.[133] A more recent study, from 2014, surveyed 22 subjects with motor disorders related to Parkinson's, and found a significant reduction in reported symptoms during an evaluation that took place 30 minutes after smoking cannabis.[134] Another study, also from 2014, found that a small number of patients experiencing rapid eye movement sleep behavior disorder—a symptom of Parkinson's associated with talking or walking in one's sleep—found significant relief after taking a CBD supplement.[135]

Most of these investigations have focussed on small sample sizes, with inconsistent means of measuring patient outcomes, and there are relatively few studies that looked directly at markers of cannabinoid activity. Moreover, researchers have worried about how cannabis interventions can affect other issues affecting people with Parkinson's, including mood and cognition.[136] As of this writing, Parkinson's is a qualifying condition for medical cannabis in Arizona, Connecticut, Florida, Illinois, Maine, New Mexico, New York, Pennsylvania, and Rhode Island, and while the body of data supporting its efficacy in treating Parkinson's is currently modest, it continues to grow.

Alzheimer's disease

Alzheimer's disease is a serious neurodegenerative condition, typically identified among older people experiencing cognitive decline. The consequences include major impediments to memory, cognition, and learning ability, and these can lead to serious disruptions to the lives of patients and the people that care for them. Alzheimer's disease is the sixth leading cause of death in the United States, and the estimated 18.4 billion hours of unpaid care given to people with Alzheimer's is $232 billion.[137]

Considerable gaps still exist in our understanding of Alzheimer's, but its chief markers in the brain are the build-up of b-amyloid proteins, and the hyperphosphorylation of tau proteins, which lead to cell death and impaired communication between neurons. Given the endocannabinoid system's negative-feedback role in slowing some nerve signals, there is some evidence that it can help to protect neurons from the consequences of b-amyloid accumulation, and so it may have a role in overcoming the neuroinflammation, excitotoxicity, and oxidative stress associated with this disease. At the same time, because the cannabinoids may have a role in promoting neurotrophin, an agent keeping brain cells healthy and vital, they may be helpful in reversing the problems with nerve signaling that are prominent among Alzheimer's patients.

Much of the hope that cannabis therapy offers for the treatment of Alzheimer's has to do with the effect of cannabinoids on b-amyloid proteins, which accumulate and cause cell death when they are improperly broken down. Authors of a paper published in 2015 tried to track this phenomenon by administering injections of THC and CBD extracts into the abdomens of mice, which had been genetically altered to produce an Alzheimer's-like effect on b-amyloid protein build-up. This appeared to reduce inflammation markers and

excitotoxicity in the mice's nerve tissue, leading to significant improvements in memory.[138] In 2016, researchers at the Salk Institute for Biological Studies, in California, found that the process of b-amyloid protein buildup could be prevented by slowing down the release of 5-LOX, a proinflammatory enzyme, through the activation of CB1 and CB2 receptors. Cells exposed to THC were found to have reduced b-amyloid protein levels, which lowered the associated inflammatory response, making them more likely to survive.[139]

There is substantial evidence that THC may have a role in inhibiting the aggregation of b-amyloid proteins, and thus slow the progression of Alzheimer's. The potential role of cannabis for treating this disease is nevertheless controversial, and doctors have sought to emphasize that it may still pose more harm than benefits, especially since people likely to seek out cannabis therapy for Alzheimer's are likely to be middleaged or elderly. Further advice on treating elderly patients with cannabis can be found in Chapter 15.

15

ELDERLY CARE

According to a study published in 2016, cannabis consumption between the years 2006 and 2013 increased by over 50% among adults aged 50 and older, and more than doubled among those aged 65 and older.[140] Though the growth of recreational use is a major part of this trend, the social and legal restrictions on medical cannabis have also changed a great deal in recent years, and many elderly patients have begun to contemplate it as a treatment option for arthritis, chronic pain, cancer, or diabetes, or for neurologic conditions such as Alzheimer's disease, and for spasticity associated with Parkinson's disease. This is an encouraging trend to anyone for whom cannabis represents a cheaper and safer way to address these conditions, and with fewer side effects than many conventional medicines.

At the same time, there are substantial safety concerns that seniors considering medical cannabis should keep in mind. The first of these are fairly obvious: THC is an intoxicating compound, and it is unsafe to drive, cook, operate machinery, engage in strenuous physical activity, or use delicate tools while you are impaired. Consuming a product containing THC can lead to short-term attention and memory problems, reduced agility and coordination, increased reaction time, and higher rates of drowsiness or fatigue.

The consequences of irresponsible use can be heartbreaking. In the U.S., reports published in 2018 by the Insurance Institute for Highway Safety and the Highway Loss Data Institute found that car collisions increased by up to 6% in Colorado, Nevada, Oregon, and Washington—states that had recently legalized recreational cannabis—compared with neighboring states, where the substance was still restricted.[141] According to a 2017 study from France, drivers under the influence of cannabis multiply their risk of causing a fatal accident by a factor of 1.65.[142]

It's always a good idea to seek out advice from your doctor and a qualified cannabis specialist on how a given product may interact with other medications. The sedative properties of benzodiazepines, barbiturates, and opioid-based pain

medications can often be significantly intensified by the effects of CBD or THC, as well as terpenes such as linalool or myrcene. Also, because the active ingredients in cannabis can interact directly with CYP450, an enzyme produced by the liver, cannabis can reduce the effectiveness of antibiotics or seizure medications. People with heart conditions taking blood thinners such as warfarin should be particularly careful, since cannabinoids can block the metabolic pathways of these drugs, so that they remain in your system for longer than intended, and can lead to an increased incidence of bleeding, bruising, or skin necrosis.

Lastly, even if you are consuming cannabis in a controlled environment, cannabis can lead to a greater risk of falls at home. This is one of the reasons I would suggest inexperienced users take their first few trial doses close to bedtime—especially if you are taking edibles or oral-mucosal tinctures, since the effects of these are slower and can be less consistent. (For an extended discussion of dosing, see Chapter 16.) No matter what route of administration you choose, I would urge you to learn as much as you can about the cannabinoid and terpene profile of the item you are considering; notwithstanding the demand among recreational users for cannabis with the highest possible density of THC, a well-run dispensary will have products with less sedating or otherwise intense effects. These will invariably be easier to titrate until you've found a dosage level that brings relief.

16

DOSING TIPS, AND WHAT TO CONSIDER WHEN CHOOSING A CANNABIS PRODUCT

When considering the advantages and possible downsides of medical cannabis, it's worth explaining how we describe its risks compared to other medicines.

For a substance like heroin, the established LD50 level—describing a lethal dose for 50% of the population—is approximately 22 milligrams per kilogram of body weight. By comparison, the LD50 for ibuprofen is about 636 milligrams per kilogram of body weight. It is 192 for caffeine, and 50 for nicotine. For a cannabinoid like CBD, the figure is 1,500 milligrams per kilogram of bodyweight. For THC, the necessary dosage is above 3,000 milligrams per kilogram of body weight.

To extrapolate, this means that an adult weighing 70 kilograms (about 154 pounds) could theoretically consume 17 kilograms of exceptionally potent marijuana—enough to fill a large bathtub—in about fifteen minutes, and still not meet a toxicity threshold. (As I mentioned in a previous chapter, this is partly due to the fact that cannabinoid receptors—despite being relatively abundant throughout the nervous system—are scarce in the brain stem, which is responsible for vital respiratory functions.) In 2015, the Centers for Disease Control reported a total of 52,404 deaths from drug overdoses in the United States, the vast majority of which were related to opioids—particularly prescription medications, which led to 20,101 fatalities. Heroin was the attributed to 12,990 fatal overdoses. Cannabis was attributed to precisely zero.[143]

None of this is to suggest that cannabis is a risk-free substance. On the contrary, even when the psychoactive properties of cannabis are ruled out, there are some people who expose themselves to unacceptable risk by consuming it.

This includes anyone who is pregnant or nursing. In 2018, the American Academy of Pediatrics published a thorough review of the existing safety data, in which they declared that new or expecting mothers should be advised against

consuming cannabis in any form.[144] While long-term research is lacking, and ethical concerns would make random-controlled trials difficult, the epidemiological support for this conclusion is immense. Unlike in adult brains, CB1 receptors in the brain of a fetus are located mostly in the amygdaloid complex, the hippocampus, and the ventral striatum, all of which are important for emotional regulation, cognition, and memory, and due to their low molecular weight and high lipid solubility, the active ingredients in cannabis can enhance the permeability of the placenta, and transfer easily into human milk. As a result, cannabis has the potential to alter circulation patterns in the womb, and consuming it during pregnancy can lead to problems with fetal growth. Pregnant women who smoke marijuana were found to have five times the carbon monoxide levels in the placenta compared to those who smoked tobacco; this all but guarantees an impaired respiratory exchange with the fetus. Consuming it while nursing can disrupt neural development, and profound impact early neonatal behavior.

People taking antibiotics, seizure medications, or heart medications—including blood thinners—should consult a trained cannabis physician prior to initiating cannabis therapy. Many cannabinoids can alter the structure of compounds in our liver known as cytochrome P450 (CYP450) enzymes, which are responsible for degrading toxins and filtering them out. When CBD binds to CYP450, it renders the enzyme less effective, and less available to break down other substances; antibiotics and some seizure medications can be less effective as a result. At the same time, cannabinoids can block off the metabolic pathways of blood thinners such as warfarin, so that the drug remains active for longer than intended, and side effects such as bleeding, unusual bruising, and skin necrosis can be much more pronounced.

Another group to whom cannabis is very likely to do more harm than good is people with a family history of schizophrenia. As with studies into cannabis and pregnancy, there is a noticeable lack of research involving either randomcontrolled investigations of the link between cannabis use and prolonged psychosis, or longitudinal trials that can conclusively rule out other environmental factors. At the same time, there is substantial epidemiological evidence that psychotic episodes can be more frequent, more intense, and more difficult to treat among cannabis users. All of this may sound like common sense—most high school drug education classes mention the mild hallucinations, distortions in space or time, and heightened anxiety levels brought on by cannabis consumption—but not everyone takes this advice to heart. What's doubly unfortunate is that adolescents—including those who might be tempted to ignore their teachers' and drug counselors' advice—are particularly vulnerable

to the psychiatric risks of cannabis. The developing brains of young people are especially fragile, and cannabis can interfere with the work of neurotransmitters like dopamine or GABA, whose dysfunction is closely tied to schizophrenic symptoms. For these reasons, I have never suggested cannabis as a treatment option to people who might also be at risk of psychotic disorders. I also think it is particularly unwise to prescribe cannabis to children or teenagers.

If you've discussed medical cannabis with a specialist, and are confident in your understanding of how it can help with a given medical condition, there are still a few things to keep in mind when determining appropriate dosage levels. Different routes of administration have different advantages and risks, which should be constantly kept in mind when making these decisions.

To begin with, it's worth knowing as much as possible about the cannabinoid contents of a given product before you consume it. The robust demand among recreational users for cannabis with the highest possible THC content has prompted many dispensaries to offer strains with overwhelming effects that medical users neither want nor need. As I mentioned in the previous chapter, cannabis that is smoked or vaporized will be relatively easy to titrate, since the effects are felt so quickly, but the surface area of a user's lungs—which can obviously vary—and the length of inhalation are both complicating factors. All of this should be measured against the cardiopulmonary risks of smoked cannabis—which are increased with the use of butane lighters—and the size of the average inhalation, which provides between one and ten milligrams of cannabinoids. For patients who choose to smoke or vaporize their cannabis, the most practical approach is to start with one inhalation, and continue every fifteen minutes, until they feel the desired relief.

Another group that should be particularly wary of dosage levels are those who use cannabis tinctures or edibles. To begin with, edible products sold at a typical dispensary can vary wildly in quality. This is partly because so many of these products are prepared with undiscriminated cannabis leaf tips and stems, which are discarded during the trimming process to make the stand-alone flowers look cleaner and more refined. As a result, during the extraction process for many commercially available edibles and tinctures, different strains are often mixed together, which means a single box of chocolates or gummy candies can have extremely divergent effects from dose to dose, as well as from patient to patient. The effects of edibles can be made somewhat more predictable if you make your own cannabis oil—using a single strain—but not everyone has the time or the skill set to do this at home, and even then, a considerable amount of trial and error will be needed before you figure out what works.

The smartest strategy you can take with either edibles or oral-mucosal

tinctures is to, “start low and go slow,” watching out for potential side effects, and always aiming for the minimum effective dose. (It can take up to two or three weeks before you feel the full impact of some products.) I routinely suggest taking a first trial dose at bedtime, when the potential sedation and disorienting qualities of CBD or THC are less of a risk. Currently, there are no standard dosing guidelines for CBD or THC. Most of our strongest data regarding dosing has been from studies looking at isolated samples of these compounds—as opposed to full-spectrum products, which frequently require lower doses, as a result of the Entourage Effect. To give one example: CBD isolates—such as the newlyapproved, plant-based CBD isolate Epidiolex®—have shown to be effective in treating rare genetic seizure disorders, at doses between 10–20 milligrams per kilogram of bodyweight.

Despite this, we know that much lower doses can be effective for a variety of ailments. I currently suggest using a full-spectrum product and starting at ½ milligram per kilogram of body weight per day—or 1–2 milligrams per 10 pounds of body weight per day. This can be slowly increased by ½ milligram/kilogram or 1–2 milligrams per 10 pounds of body weight until a desired effect is achieved. Doses up to 1500 milligrams of CBD daily have been shown to be safe and well tolerated in humans.

Higher doses are frequently required for CBD isolates, and I typically suggest starting between 2–5 milligrams per kilogram of body weight, or 5–10 milligrams per 10 pounds of body weight. For THC dosing, it is even more important to start “low and go slow” to avoid unwanted psychoactive properties. For those considering THC products, I suggest starting between 5-10 milligrams daily, again with the dose being given at night in order to reduce unwanted side effects of fatigue, drowsiness, or dizziness. This can slowly be titrated up by five milligrams daily, until the appropriate dose is reached. (See Chapter 4 for more details on the different routes of administration, their onset and duration of action and whether repeat dosing is ever required.)

The trickiest route of administration to suggest dosage for would probably be topical cannabis products. Luckily, these products are also generally very low-risk. The best way to titrate with these treatments would be to apply them every two to four hours, keeping in mind that some terpenes and topical additives in these products may themselves cause mild irritation of the skin. The skin is the largest organ system of the human body, and is also rich in cannabinoid receptors, and while cannabis-based skin balms, salves, lotions, and creams show a great deal of promise for skin irritation, inflammation, or moderate sunburns, the bioavailability of active ingredients in cannabis varies very widely through this method.

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