CANNABIS REVEALED

HOW THE WORLD'S MOST MISUNDERSTOOD PLANT IS HEALING EVERYTHING FROM CHRONIC PAIN TO EPILEPSY

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Cannibis Revealed

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Table of Contents

Foreword

It has now been 20 years since the landmark ballot initiative in the state of California that enabled patient access to cannabis for medical purposes. After litigation that was battled all the way to the 9th Circuit Court of Appeals (Conant vs. Walters), it was ruled that physicians had the right to discuss the pros and cons of cannabis, and even recommend its use to their patients. When the US Supreme Court declined to hear the case, its impact reverberated nation-wide. As is often the model with any social movement, California blazed a trail that became a model for other states and nations on this important issue. A majority of states now have legal access to cannabis for medical usage in some form. While cannabis remains an illegal, forbidden Schedule I substance under federal law, this state-by-state "experiment" is being allowed to play out, but this situation could change.

It is important to understand these developments in context. Cannabis, along with other herbal medicines, has been utilized by humans for healing purposes for millennia. It is only in the last 75 years that moral imperatives, but not science, have decreed its prohibition. Examining the issue in this light, cannabis has been the scapegoat of a historical aberration and one that may be reaching its conclusion after a long and costly "War on Drugs" both in financial respects and, more importantly, in terms of the human suffering that it has produced.

The battle is not over, however, despite the acceptance of the concept of cannabis as medicine by the overwhelming majority of the populace. Politicians are not yet fully on board with the concept and neither is the medical community, largely as the result of ignorance borne of a total lack of education on cannabis and the endocannabinoid system in medical schools. Each physician who is confronted by her first patient who asks the question, "Would cannabis help?" must decide whether to investigate the matter on her own, or merely let the question go unanswered, or be dismissed with some snarky remark that there is simply not enough information available with which to render a decision. As you will note in this book, Bonni Goldstein, MD was confronted with the same dilemma, but chose the path of educating herself so that she could best help her patients with their intractable medical problems. The results have been amazing and have produced remarkable benefits to those afflicted and their extended families. Many of us that work with such patients are constantly struck with the fact that it is only when an individual, a family member or close friend is touched by some dire medical need that finds relief in cannabis that hardened opinions against its use are softened or morphed into acceptance.

So, what is a patient or caregiver to do? Cannabis remains a subject where it

is more likely than not that the patient will need to educate their doctor first. Such a task requires good tools, and I can think of few better than this book. It is affirming and refreshing to now possess a resource that presents the scientific facts on cannabis in such an accurate and accessible form. The reader will gain the knowledge necessary not only to understand cannabis and the endocannabinoid system, but also to make informed decisions on how to apply that knowledge to the treatment of myriad conditions where "conventional medicine" has all too frequently failed. We should be clear that cannabis is not miraculous. It may or may not help treat a given condition, but what is truly remarkable is how often it is of benefit, providing just enough relief so that a patient can properly cope with the challenges of their particular situation, and get on with life again as an active participant rather than a passive observer relegated to the sidelines. That is no small achievement.

I know Bonni as a gifted and compassionate healer and it pleases me greatly to know that her knowledge and experience can now be shared on a greater stage. Read, learn and enjoy!

Ethan Russo, MD

Author's Note

First do no harm.

I don't recall exactly when I learned my mother had suffered from seizures. I think I was in high school when my mother finally talked to me about her medical history and, while I always had intimations, I felt shocked to hear about it. When I look back on my childhood I see clues, despite her keeping it a secret from just about everyone.

My parents were homebodies and devoted to their children. My mother made dinner every night, my father came home from work and played with us outside, if the weather was nice, and both were always supportive of me. I was always smaller than my peers, got good grades and aimed to please. I was consistently told I was intelligent which I think made me want to achieve even more. I wasn't interested in being social: I basically did my own thing, happily reading voraciously. I first began dreaming of becoming a doctor when I was eight years old after watching the television show *Emergency*. I decided then that medicine was going to be my career and, ever earnest, I never once questioned or varied from the path that I had to take to get there.

My mother didn't drive when I was a little girl growing up in Brooklyn. Because there was an abundance of public transportation, it didn't seem that strange, and most of my friends' mothers didn't drive either. When we moved to the suburbs in New Jersey, I noticed that my mother was the only one who didn't drive. We never talked about it, and eventually my mother did get her driver's license, but it was many years before I learned the real reason she hadn't for the early part of my childhood.

About the same time that I began dreaming about being a doctor, I also became aware that my mother took medications every night. Two big prescription bottles sat in the upper cabinet next to the kitchen sink and, whenever I asked about them, she gave a vague answer. I remember getting a sense that this wasn't something she wanted to talk about, so I stopped asking. A few years later, when I was a teenager, I was standing next to her by the kitchen cabinet where the medicine bottles were placed and asked her again about her medications, completely unaware of the story that she finally decided to share.

That day, she told me that when my sister was two years old and I just an infant, she had her first grand mal seizure in a Brooklyn playground and then two more seizures over the next few days. She eventually went to NYU to see a neurologist and while in his office she had another grand mal seizure. Hospitalized immediately, she, my father, grandmother and uncles were told that she might die. Diagnostic studies of the brain in the early 1960s were quite limited and the doctors did not know what was causing the seizures. Started on

phenytoin (Dilantin) and phenobarbital, she responded positively and was told to continue taking them for the rest of her life.

My grandmother, an uneducated and superstitious immigrant, was in complete denial that my mother had epilepsy. She was terrified and embarrassed at the same time. Because of this, my parents became tight-lipped about what had happened. It just was not discussed or shared with anyone, and for most of my childhood I was unaware of her suffering.

I learned much later that even though the medications stopped her seizures, the side effects were difficult to tolerate. She became excessively hirsute and had significant lethargy and fatigue, making the care of two small children particularly challenging. She also had severe gingival hypertrophy, an overgrowth of gum tissue and a common side effect of phenytoin, which led to a lifetime of problems with her gums that still continues. I recall being in middle school and finding out that my mother had to have oral surgery for a terrible problem she was having with her gums. She stayed in bed for days with severe pain after the procedure. I can still see her there with ice on her swollen cheeks, black and blue, unable to talk or eat. Little did I know at the time that this was a result of her seizure medication.

After my sisters and I were in high school, my mother decided that she just couldn't tolerate the side effects of the medication any longer and that she was finished with them. She didn't consult her doctor or even gradually wean herself off the drugs, but rather just stopped taking them. Fortunately, she had no repercussions from this arguably risky decision and remains seizure free today.

Meanwhile, I continued to pursue my medical degree and eventually became a doctor working primarily in pediatric emergency medicine and urgent care. I loved my work saving lives at the county hospital and teaching medical students and residents, but once I had my son, things changed. I had thought I could manage working nights and being with my son during the days, but after a few years it grew more and more difficult as I didn't feel truly present when home with my family. Given my skills in educating and communicating, I was a very good pediatric ER doctor, but my frustrations came from the exhaustion of night work and from trying to be a caring physician in a broken system. It wore me down.

After taking a leave of absence, a sick friend asked me about medical cannabis, putting it on my radar. Once I started reading the scientific literature, I grew incredulous that despite the discovery of the endocannabinoid system, the most widespread receptor system in humans, and my years of science-based education and medical training, I knew absolutely nothing about cannabis and how it works.

Intrigued, I continued to read and study everything I could find about cannabis and soon decided to work part-time in a local medical cannabis clinic.

I was surprised to find that the patients I met were just everyday normal people who went to work, who had families and who had medical conditions that were not responding to conventional medications or the traditional Western medical interventions in which I, too, was trained. These were people who simply wanted a better quality of life.

I haven't looked back since.

Cannabis was not medically available or used as an anticonvulsant during the years that my mother took anti-seizure medications. In 1970, five years into her epilepsy diagnosis and treatment, the federal government classified cannabis as a Schedule I controlled substance with the passage of the Controlled Substance Act. Defined as a "drug or other substance that has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and is lacking accepted safety for use of the drug or other substance under medical supervision," the Schedule I continues to this day. It has virtually shut down all research on the multitude of compounds in cannabis which we now know to have low risk for abuse, to have true and proven medical use, and to have an excellent safety profile, especially with medical supervision.

Scientists had started significant cannabis research in the 1960s and were gaining knowledge on the phytocannabinoids, but this act by Congress completely closed the door on advancing cannabinoid science. After the discovery of the endocannabinoid system in the late 1980's, investigations in the field have exploded over the past two decades. We are finally catching up on research that should have been completed years ago.

I am angry that my mother suffered, and continues to suffer, from the side effects of medications that she took to alleviate her epilepsy. These side effects caused problems that persisted throughout her life, even after she stopped taking the drugs. My mother's suffering was in part due to the propagation of false claims about cannabis based on ignorance and greed. The false claims continue, despite the fact that millions of patients who could be helped by cannabis continue to suffer with medical conditions that are not responding to conventional treatment, and millions more grapple with intolerable side effects of those treatments.

As a physician, I took an oath to "do no harm." After treating thousands of patients seeking relief with medical cannabis, I can assert that the compounds in cannabis relieve unnecessary suffering with little to no adverse side effects.

I have witnessed sick and desperate patients have a complete turnaround in the quality of their lives. Cannabis medicine must be available as an option or alternative to current first line treatments, especially if those treatments have harmful or potentially fatal side effects. If a pharmaceutical with the properties of cannabis were synthetically created and introduced today, the medical community would embrace it with open arms and tout it as a miracle drug.

It's been 50 years since my mother developed epilepsy when I was only a child, and I get emotional thinking about her needless suffering. Many physicians find their vocation from early experiences with ill relatives and friends. While I had little awareness of my mother's struggles with seizures and medications, I find as a physician recommending medical cannabis to my patients, that her life and experience have indeed informed mine. I wish that medical cannabis had been available to my mother.

I cannot undo what she endured. I can help others, though, by sharing the current knowledge about cannabis and cannabinoid science.

I have written this book so that you and your loved ones, who may be suffering as my mother did, can move past the false propaganda that continues to this day and understand how cannabis is medicine.

Prologue

As a little girl, whenever I was alone – outside digging in the dirt or absent-mindedly swinging on the swing set, splashing or playing in the bathtub – I would start humming a tune. I'd start softly and then grow bolder, add in little trills and jazzy riffs, each note a bit louder than the next.

As I got older, I'd experiment with dropping my voice down to get to the lower notes and more dramatic effects. I had been exposed to singers like Judy Garland, Billie Holiday, Frank Sinatra and Nat King Cole, and then to songwriter artists like Joni Mitchell, Bob Dylan and Carole King. I listened to James Taylor, Cat Stevens and 60s Motown, and I recall at age twelve or thirteen thinking that Phoebe Snow was the ultimate in cool. Singing brought me freedom and joy, always, or at least until the pain started, and I was diagnosed with rheumatoid arthritis.

Over those years and the many that followed, in my late teens and early twenties, I didn't do that much singing, but on the occasions when I did, singing was one of the few things I could do to forget almost completely the way my body felt. During those moments, I tasted a little bit of freedom and was released from the pain and the loss of everything I used to be – all of my former life – even for a few minutes.

I have noticed lately, though, that during the process of taking my cannabis medicine that I am humming again, albeit weakly with little breath or power. The humming grows stronger as I feel the medicine move through my system and I find myself adding jazzy riffs right and left, treating my voice like a slide trombone. I can go mournfully low and tragic like Billie and then trill upwards sweet and high like Ella. I imagine myself as sultry and sassy, as confident as Peggy Lee.

It's as if cannabis has helped me to unlock the box in which I've kept my own personal songbird. This may be a small thing, but if anyone knows how it feels to be trapped in a constantly malfunctioning body, they would realize what an enormous gift it is to feel well, to feel strong and capable at something again for the first time in over a decade. I was locked in a prison of illness and pain, and cannabis unlocked the door for me to break free.

Elise R., as told to me in February of 2016 and whose story appears on the following pages.

How To Use This Book

I have spent the greater part of the last decade educating and explaining cannabis as medicine to patients, politicians and medical professionals. In order to understand how cannabis can do all that it is touted to do, you must first understand the plant itself.

Chapter 1 discusses the many different compounds in cannabis and their medicinal properties. Chapter 2 explains our endocannabinoid system and how cannabis compounds interact with it. Diseases associated with an imbalance of the endocannabinoid system are also discussed. The safety of cannabis use is discussed in Chapter 3 with special considerations discussed in Chapter 5.

The bulk of the book is devoted to Chapter 4, How to Use Cannabis as Medicine. The goal of this chapter is to help you to understand the different cannabinoids and cannabis preparations, as well as dosing.

Chapter 6 discusses the multitude of ailments where cannabinoid medicine may play an important role. Interspersed throughout the book are incredible stories of patients who have had success with using cannabis medicine. These patients were able to overcome medical conditions that were negatively affecting their quality of life and they were all so eager to share their journey that led them to cannabis treatment.

The appendix includes a "History of Cannabis" timeline, a chart that explains the effects of cannabis by body system and the pharmacokinetics of cannabis medicine.

At the end of the book there are three charts that readers can use as references to understand the many facets of cannabis medicine. The first is a chart of phytocannabinoids, the second is a chart that explains the many terpenoids found in the cannabis plant and the third contains practical information to help with dosing and navigating the various cannabis products available to patients.

Gavin's Story

I sensed true desperation almost immediately when I met with Gavin and his family. The despair was nearly palpable, even in Gavin's two grandmothers who had accompanied them to the office. Gavin himself appeared oblivious to his surroundings, made little to no eye contact and was very hyperactive and distracted, moving around the office the entire time. A cute child wearing a little fedora and glasses, his face showed little affect and we made no connection. "We need help so badly," the small group said to me, "we can no longer live like this."

Rebecca is a stay at home mother with a special education degree whose first child Gavin was born six weeks early. While he had low muscle tone, something you'd expect from a preemie, he also didn't reach his early milestones and, at around age two, Gavin's health and development began to really fall apart. He was nearly two when he walked and had little to no language at age three. Ultimately diagnosed with complex partial seizures, cerebral palsy and an unknown genetic anomaly, as well as cyclical vomiting and autism, Gavin was prescribed the anticonvulsant levetiracetam (Keppra) for his seizures. He was three years old, and the effects were immediate.

While the seizures stopped, Gavin's autistic behaviors increased, and within two months his meltdowns became uncontrollable. Rebecca and her husband had read about "Keppra rage," a well-documented side effect, but they wanted to control the seizures and were hesitant to take him off of the drug or add another one. During this time, Rebecca saw the CNN documentary "Weed" and began to explore cannabis as a possible treatment. When she asked Gavin's neurologist about trying cannabis, he ignorantly told her "the tar in the smoke will give him lung cancer." She was discouraged by this response but kept searching online for information and found support on Facebook. She eventually brought Gavin to my office in early 2014. With his behavior out of control, life with Gavin had become a daily struggle.

I started Gavin on CBD-rich cannabis oil, given by mouth. The effects were immediate. Within 10 days, Gavin, previously non-verbal, began speaking. The change was so dramatic that Rebecca wanted to try weaning him off the seizure medication to see if his seizures might also be controlled. She switched neurologists and found a supportive physician who helped her to wean Gavin off the drug over five months. When he was completely off the drug, an initial EEG showed some seizure activity, but Rebecca asked for three months to adjust the dosage of CBD before trying other pharmaceuticals. The subsequent 48-hour EEG showed no seizure activity and Gavin hasn't needed any further antiepileptic medications.

Although the use of CBD-rich oil for a number of months resulted in

seizure freedom, improved verbal ability and improved behavior, Gavin continued to have some unwanted behaviors related to his autism. It was at this point that we added THC-rich oil in the mornings and afternoons to help him to be calm and focused. As we hoped, his behavior improved significantly.

Rebecca still marvels at the dramatic turnaround in Gavin due to cannabis medicine. In addition to seizure control, Gavin's incredible improvements in speech and autistic behaviors thrill her the most. Although everyone who knew Gavin saw that he was quite intelligent (even the speech pathologist had given him an iPad with communication apps because they knew his capabilities), he had no real language or any imaginary play. One afternoon, soon after Gavin began taking CBD oil, Rebecca was in her bedroom folding laundry. She looked up to see Gavin walking in with the laundry basket. He placed it on the floor, stepped into it and declared, "Look, Mom! I'm an astronaut!"

Rebecca has had to experiment with the dose and ratio of CBD and THC and has ultimately found that a particular variety of CBD-rich oil combined with another variety of THC-rich oil is giving him the best results. Gavin has no adverse side effects from cannabis use. He does not experience any psychoactivity. He is able to make connections in his kindergarten class, to fit in with his peers and to transition throughout the day with ease. He is happy and thriving, and reports from school are outstanding. The speech pathologist has even taken away the iPad with the communication apps because he doesn't need it anymore!

Gavin is now five years old and his story moves me as both physician and mother. When Rebecca sent me a video recently of him reciting the Pledge of Allegiance and breaking into "You're a Grand Old Flag," I was moved to tears. Although not every patient has this level of improvement, Gavin's story is an example of why cannabis treatment must be an available option for all children with severe medical conditions. His quality of life has been improved so significantly that he is able to participate in his life fully as all children deserve.

CHAPTER 1
The Cannabis Plant

In order to understand the medicinal value of the cannabis plant, you first need to learn about the many compounds that are found within it. The cannabis plant is made up of over 400 chemical compounds. When you use cannabis, you are taking a mixture of natural compounds that work together to balance each other.

The Latin name of the plant is *Cannabis Sativa*, in the family called Cannabaceae and Genus Cannabis. Other plants in this family are Humulus (hops) and Celtis (hackberries). These plants share an evolutionary origin but are quite different from one another.

The cannabis plant contains biologically active compounds called phytocannabinoids, terpenoids and flavonoids. These chemicals interact with our brain and body chemistry to give certain effects. Hundreds of different cannabis varieties, or "chemovars," are grown all over the world, each containing varying amounts of the 400 different compounds, with each chemovar giving different effects.

What are Phytocannabinoids?

The term "cannabinoids" is very general and refers to a group of chemical compounds that are usually made up of 21 carbon atoms in a three-ring structure. When we add the prefix "phyto" to the word, we are specifically referring to the cannabinoids that are found almost exclusively in the cannabis plant.

The main two phytocannabinoids are THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol).

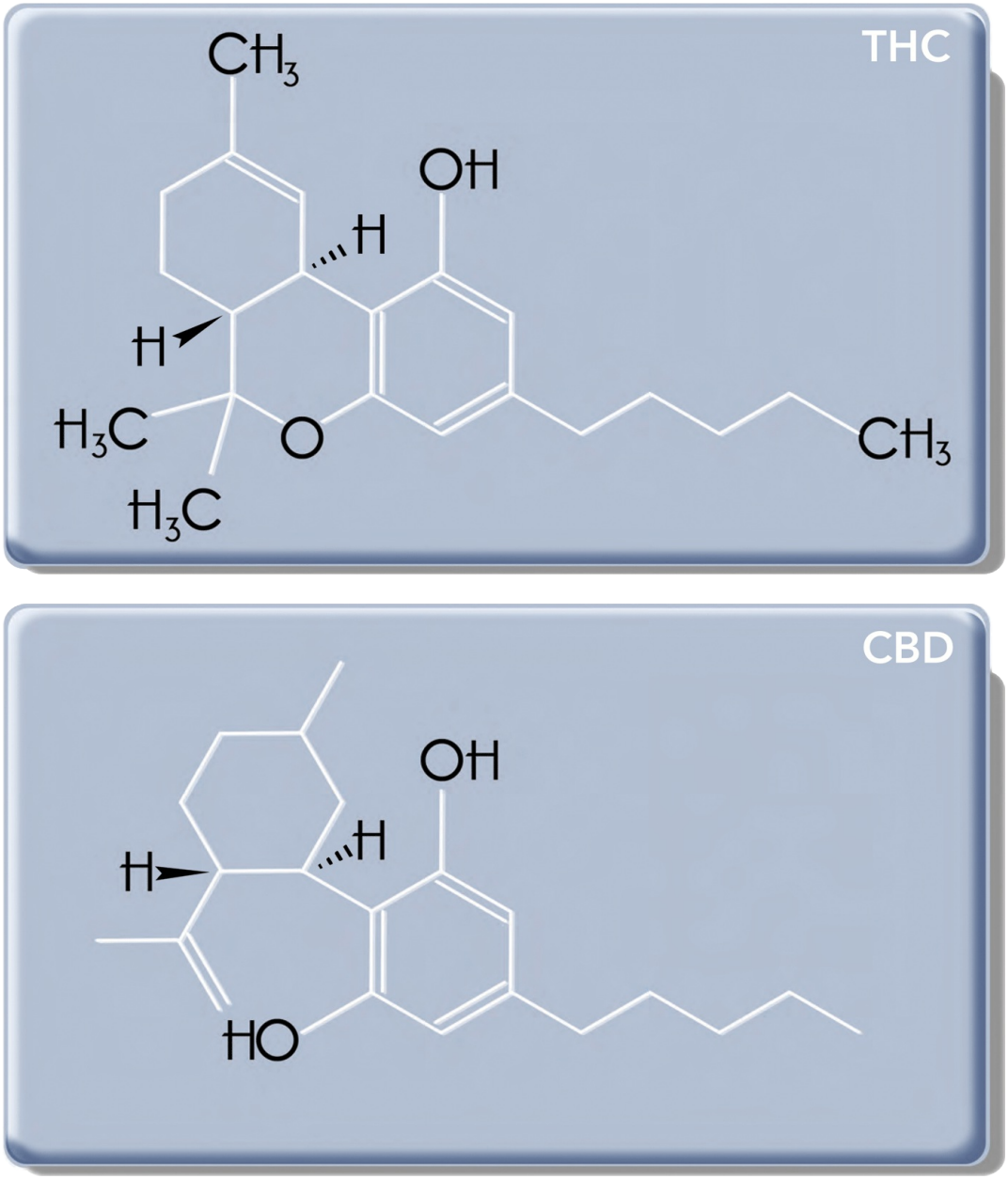


Figure 1: Molecular structures of THC and CBD

Other phytocannabinoids found in the cannabis plant, often referred to as **"minor cannabinoids,"** include cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabicyclol (CBL), cannabidivarin (CBDV), and tetrahydrocannabivarin (THCV). Future research may reveal some of these to be major cannabinoids.

The main effects of THC and CBD are summarized in Table 1.

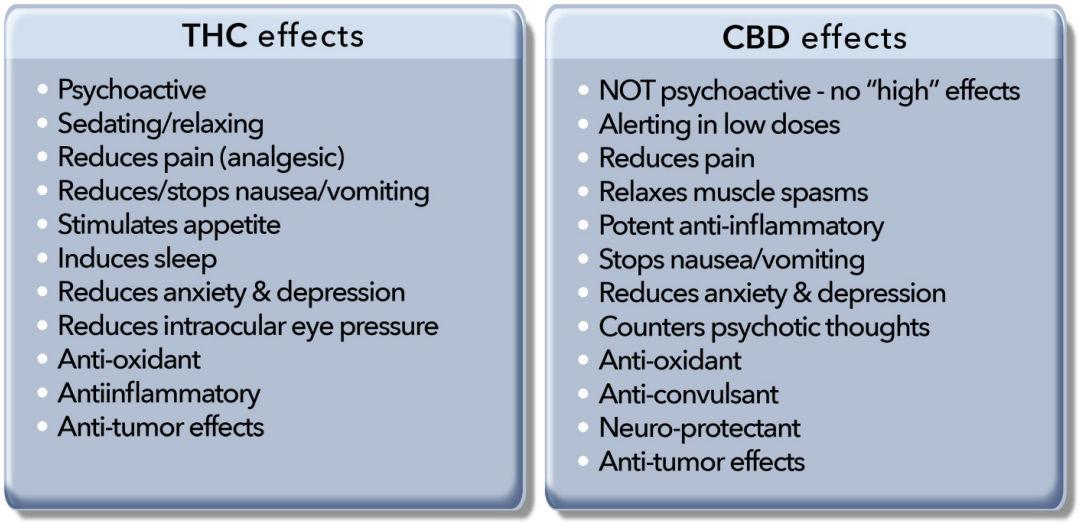


Table 1: THC and CBD effects

The average THC content of cannabis in 1972 was 1%, increasing to 4% in the 1990s, to a national average of 13% today. California cannabis testing laboratories report a current average of 18 – 20% THC content. Cannabis currently available in California dispensaries has THC content between 15% -28% with a corresponding CBD content of <1%. Concentrated forms of THC-rich cannabis can have contents up to 90%. This increase in THC content has led to a decrease in CBD content and made CBD-rich plants rare, although this is changing.

Until 2012, the potency of cannabis tested by the government and dispensaries was based solely on THC content. Now that CBD is recognized as having significant medicinal effects, testing of various cannabis products routinely reports the potency of both compounds. As you can see in Figure 2, various chemovars (chemical varieties or "strains") of cannabis are listed with their potencies of THC, CBD, and CBN. (If you are not familiar with cannabis, the plants vary in their compounds and are often given names that may reflect their chemical makeup.) Two are high in THC and quite low in CBD (Blue Dream and Sour OG), one is quite high in CBD and low in THC (AC/DC), and two have varying amounts of both THC and CBD (Cannatonic and Omrita). These plants will vary widely in their effects due to their different phytocannabinoid potencies. CBN stands for cannabinol, one of the minor phytocannabinoids. This compound is present only in trace amounts in freshly cut cannabis flowers and arises from the degradation of THC over time. As you can see in this chart, there is no CBN detected in these samples, which indicates that testing was likely performed on freshly cut flowers.

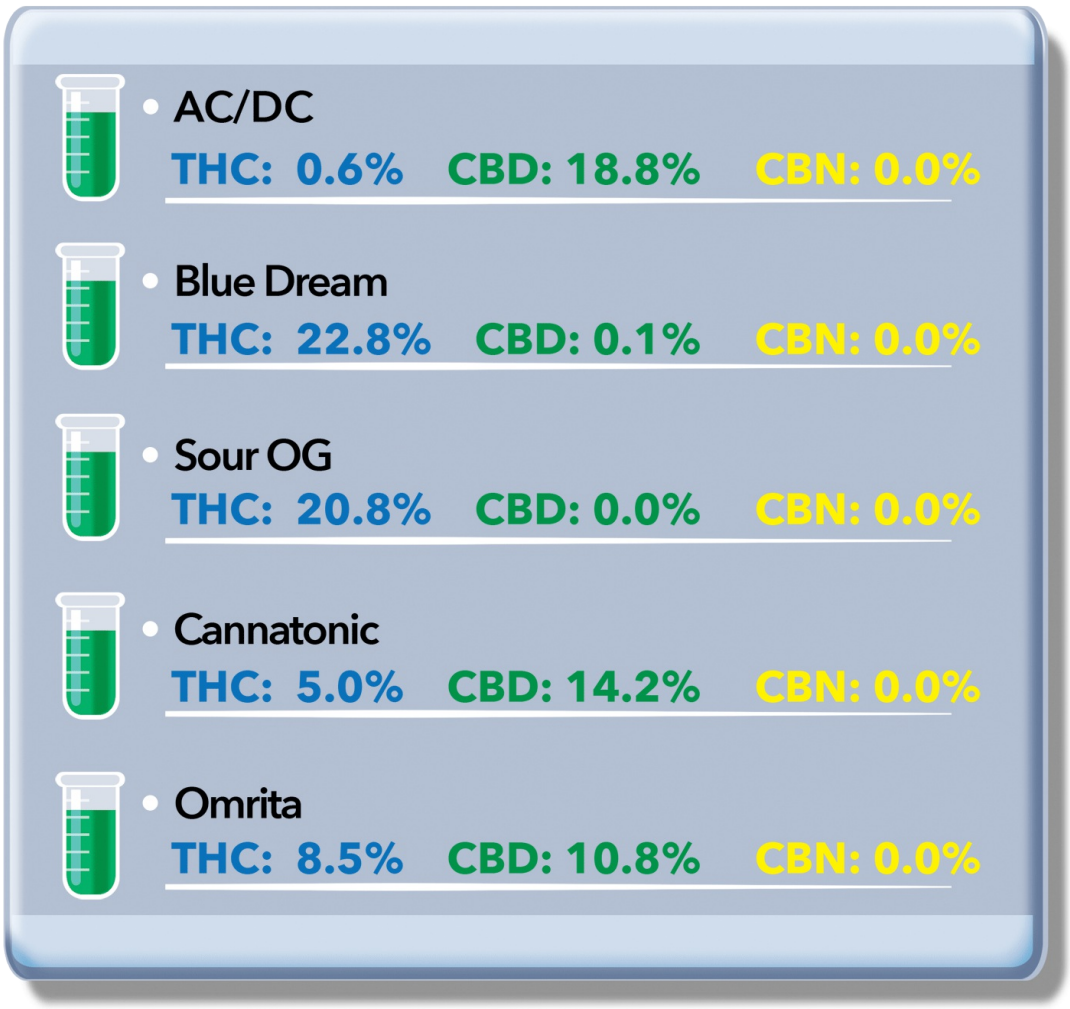


Figure 2: Cannabinoid potency test results for different cannabis chemovars

A few important notes about phytocannabinoids:

- Phytocannabinoids were initially thought to be species-specific to the cannabis plant, which meant that they were not found in any other plant species. However, phytocannabinoids other than THC have been discovered in a few other plants, namely Echinacea species, Helichysum species (sunflowers) and Radula species (liverwort).
- As mentioned above, the term "cannabinoids" is very general, and it refers to a specific group of chemical compounds. Cannabinoids are found naturally in two places: plants and animals. "Phytocannabinoids" refer to the cannabinoids that occur naturally in plants. "Endocannabinoids" refers specifically to the cannabinoids made by humans and other animals. Cannabinoids can also be synthesized in a laboratory setting; these are referred to as "synthetic cannabinoids" and are primarily used in research.
- Do not get confused about the acronym "CBD". CBD stands for "cannabidiol" not "cannabinoids". Many people incorrectly say "the

CBDs". CBD is not plural. THC is not referred to as "THCs" because it is referring to one molecule. CBD also refers to one molecule. The acronym for the word "cannabinoid" is CB, which is used mostly in scientific papers.

How the cannabis plant makes phytocannabinoids:

The phytocannabinoids are formed and concentrated in a viscous resin in the plant's glandular trichomes, the tiny, sticky hair-like formations on the cannabis flower.

Close up of the trichome of the cannabis plant

It is inside the trichomes that the phytocannabinoids are formed.

1. Geranyl pyrophosphate is the precursor to both phytocannabinoids and terpenoids.
2. Geranyl pyrophosphate couples with olivetolic acid to produce cannabigerolic acid, which is then exposed to three enzymes – THCA synthase, which will create THCA; CBDA synthase which will create CBDA; and CBCA synthase, which creates CBDA.
3. THCA and CBDA are the acid forms of THC and CBD and are the predominant compounds in the raw flower of the cannabis plant.

4. THCA and CBDA change to THC and CBD, respectively, when they are exposed to heat. This chemical reaction is called decarboxylation.

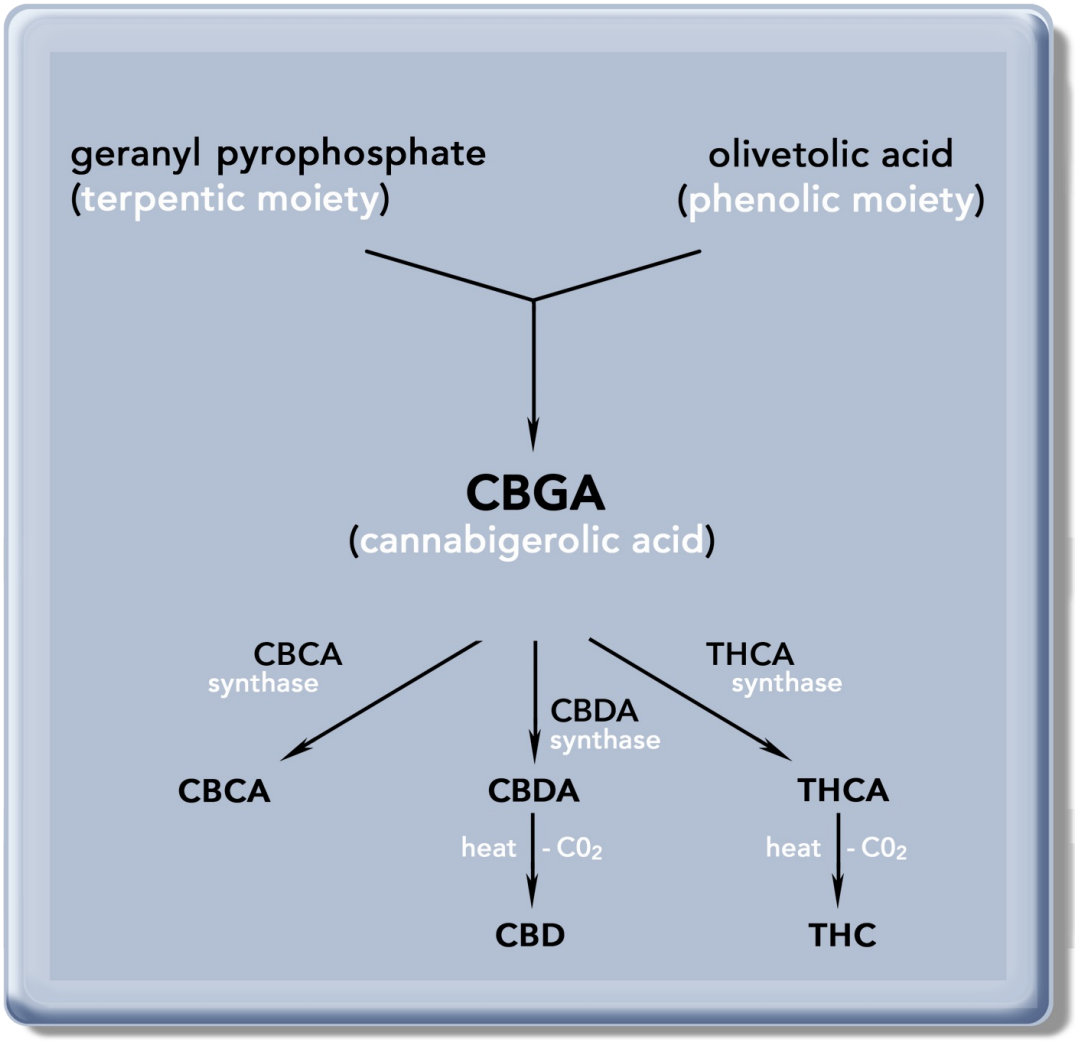


Figure 3: How the cannabis plant synthesizes phytocannabinoids

The majority of cannabis plants are genetically determined to take the pathway that leads to THCA. A small number of plants have the genetics that will lead to a higher amount of CBDA: we call these plants CBD-rich chemovars. This genetic dominance for THC explains why most cannabis is higher in THC potency and lower in CBD potency. The rampant cross-breeding of chemovars over the past three decades has also resulted in higher THC potency.

The Entourage Effect

Not all of the phytocannabinoids have been thoroughly studied, but those that

have are found to have their own medicinal effects when isolated from the other phytocannabinoids. When used together as they occur naturally in the whole plant, they balance each other in a synergistic action first called "the entourage effect" by Raphael Mechoulam, PhD. Dr. Mechoulam, an Israeli researcher, was the first to isolate THC and CBD in the early 1960s. **The "entourage effect" means that the cannabinoids work better together than when isolated from one another. The synergy can enhance effects or modulate effects beneficially.**

Example of synergistic enhancement: both THC and CBD, when given separately, have been found to have pain-relieving properties, but studies show that CBD enhances pain relief when used together with THC, compared to THC used by itself.

Example of opposing effects: CBD can decrease psychoactivity, memory loss and the increased heart rate THC can induce.

What are Terpenoids?

Terpenoids (also called terpenes) are the essential oils that occur naturally and exist in all plants, trees and flowers, including the cannabis plant. These oils give cannabis its odor, color, and flavor. About 200 terpenoids occur in the cannabis plant. **The unique combination of phytocannabinoids and terpenoids in a specific cannabis plant accounts for the varying effects felt when different types of cannabis plants are used.**

Terpenoids are made up of repeating units of isoprene (C_5H_8) and include monoterpenoids (C_{10}), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), and triterpenoids (C_{30}).

Some important facts about terpenoids:

- They are genetically controlled
- Production increases with light exposure
- Production decreases as soil fertility decreases
- U.S. FDA recognizes terpenoids as safe
- Terpenoids vaporize near the same temperature as THC
- Concentrating cannabis into hash or wax may reduce the terpenes content and may cause medicinal effects to change
- Terpenoid lab analysis is the only way to know about a certain product's terpenoid levels

Phytocannabinoids and terpenoids work synergistically to provide therapeutic effects. Terpenoids are also synergistic with each other, again

enhancing medicinal effects.

An example of a very important terpenoid is limonene. It is a monoterpene found in lemon and other citrus fruits and is the second most common terpenoid found in nature. Limonene has potent anti-depressant and anti-anxiety activity, as well as anti-tumor effects. It has been used successfully to decrease the symptoms of gastro-esophageal reflux.

This chart explains four of the most important terpenoids in the cannabis plant.

Terpenoid	Also found in:	Effects	Aroma	Synergistic with:
Limonene	Citrus rinds Caraway seeds Dill seeds Rosemary Juniper Peppermint	Potent anti-depressant Anti-anxiety Anti-tumor Chemotherapeutic (causes breast cancer cells to die) Active against acne bacteria Suppresses GERD Anti-bacterial/anti-fungal Bronchodilator	Orange Citrus Spicy	CBD – enhanced anti-depressant and anti-anxiety effects CBD & CBG – enhanced anti-cancer effects THC – enhanced anti-GERD effects
β-Caryophyllene often found in CBD-rich chemovars	Black pepper Cloves Cotton Oregano Hops	Anti-inflammatory Analgesic Gastrointestinal Relief Anti-bacterial Anti-fungal Anti-tumor *Activates the CB2 receptor located in immune system and gut (2008, Gertsch)	Woody Spicy	THC – enhanced gastric cell protection CBD – enhanced anti-inflammatory effect
Linalool precursor ingredient in formation of Vitamin E	Lavender Citrus Birch Coriander Rosewood	Anti-anxiety Analgesic Anti-convulsant Sedating, calming Active against acne bacteria Anti-cancer	Floral Spicy Citrus	CBD – enhanced anti-anxiety and analgesic effect THC – enhanced sedation and analgesic effect CBD/THCV/CBDV – enhanced anti-convulsant effect
β-Myrcene most common terpenoid found in cannabis not found in hemp	Mango Hops Bay leaves Lemongrass Eucalyptus	Sedating Muscle relaxant Analgesic Anti-oxidant Anti-cancer Anti-inflammatory Anti-depressant Anti-bacterial	Cloves Earthy Fruity	THC – may enhance effects of THC CBD – enhanced anti-inflammatory effects CBG – enhanced anti-inflammatory effects

Some examples of known synergies between phytocannabinoids and terpenoids:

- THC + CBD + **β**-Myrcene + **β**-Caryophyllene = Pain Relief
- THC + **β**-Myrcene + **β**-Caryophyllene + Pinene = ADD relief

- CBD + CBN + Limonene + Linalool = Insomnia and Anxiety relief

Terpenoid Testing

Cannabis plants can be tested for their terpenoid profiles as well as phytocannabinoid content. The terpenoid makeup of the plant is like a "fingerprint" for the chemovar. Different growers may be growing the same varieties but calling them different names, or they may be calling chemovars the same names yet terpenoid testing reveals that they are different. The terpenoid profile allows for detailed comparison of varieties and is very important to patients who find relief with one particular chemovar. If you know which terpenoids and terpenoid combinations are helpful for your condition, you can check terpenoid testing results to see if a certain product will be likely to be effective.

What are Flavonoids?

Flavonoids are compounds that give plants their pigmentation, filter ultraviolet rays, attract pollinators, and prevent plant disease. About 20 flavonoid compounds have been found in the cannabis plant. These compounds are classified as aromatic polycyclic phenols and have a 15 carbon skeleton.

Flavonoids have been shown in laboratory studies to have anti-inflammatory and antioxidant properties. They also have anti-fungal, anti-bacterial, anti-viral, anti-cancer and anti-allergic activity. Several studies in humans report the following benefits of flavonoids:

- Dietary flavonoid intake in the form of green tea decreased the risk of gastric cancer in women
- Intake of flavonoids were protective against smoking-related cancers
- Intake of flavonoids (anthocyanidins from berries and flavanols from green tea and cocoa) may lower the risk of type 2 diabetes and cardiovascular disease

Three of the main flavonoids that have been found in the cannabis plant and their properties:

Flavonoid	Medicinal Properties	Also found in
Quercetin	Potent antioxidant Anti-viral Anti-cancer effects	Red wine Green tea Berries Onions Buckwheat tea
Apigenin	Anti-anxiety Anti-inflammatory	Parsley Celery Chamomile tea Celeriac
Cannaflavin A	Potent anti-inflammatory	Unique to cannabis

Sativa versus Indica?

You may have noticed I have not mentioned the terms "sativa" and "indica" in the discussion of the plant. These terms are used frequently in the cannabis industry to designate the "two" types of cannabis plants that can have different effects. Currently cannabis growers and suppliers continue to use these terms, albeit incorrectly, referring to sativa plants as "uplifting and stimulating" and indica plants as "relaxing and sedating." Some say sativa plants cause a "brain high" and indica plants cause a "body high." Most experts agree that due to extensive hybridization over the last three decades, these designations no longer apply.

If one uses the correct scientific nomenclature, *Cannabis sativa, variety sativa* refers to the hemp (fiber) variety of the plant, meaning that the genetics of this particular plant promote the growth of the fiber with very little THC production. These fiber varieties also carry the gene that allows the plant to synthesize CBD over THC. *Cannabis sativa, variety indica* scientifically refers to the variety of the plant that carries the genetics to synthesize THC instead of fiber, so called "drug" variety plants.

Aside from their genetics, cannabis plants are living entities that respond to their environment. Growing conditions, harvest time and other factors play an enormous role in the final product. This is why the same chemovar grown in different places by different growers under different conditions can result in different phytocannabinoid and terpenoid content. For instance, a chemovar grown outdoors in Northern California is likely to have a different profile than the same chemovar grown in a greenhouse in Colorado.

The best way to determine the effects of a particular plant or product is to

first evaluate the content of CBD and THC, calculate the ratio of CBD to THC, and then look at the dominant terpenoids. This assessment will be much more informative than the simple and often incorrect terms "sativa" and "indica."

Hemp-Derived CBD

There are numerous products made from industrial hemp that claim to contain CBD for medicinal purposes. It can be very confusing to patients and caregivers who see products available online that claim to be CBD products that are legal in all states.

Martin Lee from Project CBD (ProjectCBD.org) explains that there are two types of cannabis plants: hemp plants that are used for fiber and seed oil, and drug plants that are used for medicine and recreational purposes, what I prefer to call the "medicine" plants. As Lee explains, the main difference between the hemp variety and the drug variety is the content of resin. **High-resin plants contain the phytocannabinoids, terpenoids and flavonoids – all the compounds that have proven beneficial medical effects. Industrial hemp is low-resin and therefore typically low in cannabinoid content. Hemp is not an optimal source of CBD or other medicinal compounds.**

The US government has defined industrial hemp as containing less than 0.3% THC. The majority of high-resin plants, including CBD-rich plants, contain over 0.3% THC and therefore are still illegal federally and in most states. These high-resin plants are much preferred as medicine when compared to low-resin industrial hemp.

A large number of hemp plants are required in order to obtain a small amount of CBD. This increases the risks of contamination since hemp is a "bioaccumulator", which means it accumulates toxic substances from the soil. These plants can contain metals, pesticides, gasoline and solvents and, during the CBD extraction process, these contaminants may be concentrated and can be toxic. In fact, there are anecdotal reports of people getting ill from so-called "CBD" products made from industrial hemp.

The Hemp Industries Association in a press release in 2014 stated that:

> *CBD is not a product or component of hemp seeds, and labeling to that effect is misleading and motivated by the desire to take advantage of the legal gray area of CBD under federal law. Hemp seed oil does not contain any significant quantity of CBD. Hemp fiber and seed cultivars contain relatively minimal CBD and CBD production from such plants should not be considered a primary product. There are high CBD cultivars that may qualify as "hemp" under federal law, however the genetics for such cultivars are closely held by various parties, and generally hemp cultivars available to American farmers are not suitable for producing CBD.*

Source: www.thehia.org/HIAhemppressrelease/3346474

In 2015, the FDA tested products obtained through the Internet, which claimed to contain CBD. They found these products to contain either no CBD or tiny amounts of CBD that would not be effective as medicine.

I encourage my patients to avoid products that come from industrial hemp as I have found that the drug (medicine) variety of cannabis is a much more effective product when treating most illnesses. That means patients should use whole plant cannabis that is labeled properly, lab-tested, and safely extracted. There are some products that are labeled as hemp but they contain THC, other cannabinoids and terpenoids. These products may have medicinal value. Unfortunately there is still a fair amount of confusion even within the cannabis industry. Hemp products, such as hemp milk, hemp oil, and hemp seeds, which are available in most grocery stores are a beneficial dietary source of balanced omega-3 and omega-6 fatty acids and should be a part of your diet.

Sources

Al Mansouri, Shamma, et al. "The cannabinoid receptor 2 agonist, β-caryophyllene, reduced voluntary alcohol intake and attenuated ethanol-induced place preference and sensitivity in mice." *Pharmacology Biochemistry and Behavior* 124 (2014): 260-268.

Bahi, Amine, et al. "β-Caryophyllene, a CB 2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice." *Physiology & behavior* 135 (2014): 119-124.

Campos, Alline Cristina, and Francisco Silveira Guimarães. "Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats." Psychopharmacology 199.2 (2008): 223-230.

Colasanti, Brenda K., Charles R. Craig, and R. David Allara. "Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol." Experimental eye research 39.3 (1984): 251-259.

Deiana, Serena, et al. "Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ9-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive–compulsive behaviour." *Psychopharmacology* 219.3 (2012): 859-873.

Hayakawa, Kazuhide, et al. "Repeated treatment with cannabidiol but not Δ 9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance." *Neuropharmacology* 52.4 (2007): 1079-1087.

Hillig, Karl W., and Paul G. Mahlberg. "A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae)." American Journal of Botany 91.6 (2004): 966-975

Huestis, M. A. "Pharmacokinetics and Metabolism of the Plant Cannabinoids, Δ 9-Tetrahydrocannibinol, Cannabidiol and Cannabinol." *Cannabinoids*. Springer Berlin Heidelberg, 2005. 657-690.

Lee, Martin. "Sourcing CBD: Marijuana, Industrial Hemp and the Vagaries of Federal Law." https://www.projectcbd.org/article/sourcing-cbd-marijuana-industrial-hemp-vagaries-federal-law

McPartland, John M., and Ethan B. Russo. "Cannabis and cannabis extracts: greater than the sum of their parts?" Journal of Cannabis Therapeutics 1.3-4 (2001): 103-132.

Moldzio, Rudolf, et al. "Effects of cannabinoids Δ (9)-tetrahydrocannabinol, Δ (9)-tetrahydrocannabinolic acid and cannabidiol in MPP+ affected murine mesencephalic cultures." *Phytomedicine* 19.8 (2012): 819-824.

Novak, Johannes, et al. "Essential oils of different cultivars of Cannabis sativa L. and their antimicrobial activity." Flavour and fragrance journal 16.4 (2001): 259-262.

Pertwee, R. G., et al. "The psychoactive plant cannabinoid, Δ9-tetrahydrocannabinol, is antagonized by Δ8-and Δ9-tetrahydrocannabivarin in mice in vivo." *British journal of pharmacology* 150.5 (2007): 586-594.

Petitet, François, et al. "Complex pharmacology of natural cannabivoids: Evidence for partial agonist activity of Δ 9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors." *Life sciences* 63.1 (1998): PL1-PL6.

Rock, Erin M., et al. "Interaction between non-psychotropic cannabinoids in marihuana: effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews." Psychopharmacology 215.3 (2011): 505-512.

Russo, Ethan B. "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects." *British Journal of Pharmacology* 163.7 (2011): 1344-1364.

Russo, Ethan B. "Beyond Cannabis: Plants and the Endocannabinoid System." Trends Pharmacol Sci (2016) 37 (7):594-605.

van Dam, Rob M., Nasheen Naidoo, and Rikard Landberg. "Dietary flavonoids and the development of type 2 diabetes and cardiovascular diseases: review of recent findings." Current opinion in lipidology 24.1 (2013): 25-33.

Verhoeckx, Kitty CM, et al. "Unheated Cannabis sativa extracts and its major compound THC-acid have potential immuno-modulating properties not mediated by CB 1 and CB 2 receptor coupled pathways." International immunopharmacology 6.4 (2006): 656-665.

Woo HD, Kim J (2013). "Dietary flavonoid intake and smoking-related cancer risk: a meta-analysis". PLoS ONE 8 (9): e75604.

Zamora-Ros R., et al. "Dietary flavonoid and lignan intake and gastric adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Am J Clin Nutr (2012) 96:1398–408.

CHAPTER 2
The Endocannabinoid System

To those who don't believe in cannabis as medicine, I ask: "do you know about the endocannabinoid system and what medical conditions are associated with its dysfunction?" If they cannot answer this question, they are not knowledgeable enough to comment on cannabis as medicine. I joke around with my patients that I have no opinion about my car's engine, but my husband has many opinions. I know nothing about car engines (nor am I interested), but my husband knows a lot. I am not qualified to make any statements about which engine is good or bad. If you don't know about the endocannabinoid system, you are not qualified to have an opinion about cannabis as medicine until you educate yourself!

Here is just about everything you need to know about the endocannabinoid system.

In 1964 Dr. Raphael Mechoulam and his colleagues at the Hebrew University in Jerusalem isolated THC and found it to be the main psychoactive compound in cannabis. It took another 24 years to understand how THC caused its well-known effects. In 1988 Dr. Allyn Howlett and her colleagues at St. Louis University discovered the cannabinoid receptor. Using advanced scientific techniques with radioactive dye attached to synthetic THC, the researchers were able to follow where THC went in the brain. They saw that it selectively attached to a specific receptor located on the membranes of certain cells. A receptor works like a "lock" on the cell membrane, waiting for a specific "key" to bind to it, which then starts a chemical reaction in the cell resulting in a change in the message that the cell is sending. We have many other "lock and key" receptor systems in our brains and bodies, such as opioid receptors, dopamine receptors, etc. The cannabinoid receptor happened to be discovered in the quest to understand how THC works to make people high.

Scientists hypothesized that humans did not have these receptors for the "THC key" from the plant but rather we had to make our own "cannabis-like key" that worked at the receptor site. All other receptors found in humans have "keys" that we make from within such as endorphins that bind to our opioid receptors. Understanding this, researchers began to look for our "inner cannabis."

In 1992 the first of five "inner cannabis" compounds were discovered. Anandamide (also called N-arachidonoylethanolamine or AEA) was the first

cannabis-like compound to be detected. In 1995, a second compound made in our bodies named 2-arachidonlygylycerol (2-AG) was discovered. These compounds were named "endogenous cannabinoids" or **endocannabinoid**s ("endo" is Greek for "inside or within"). Several endocannabinoid compounds have since been discovered, in addition to a second cannabinoid receptor located primarily in the immune system.

The discovery of the cannabinoid receptor and the endocannabinoids caused tremendous excitement in the scientific community and research into "cannabinoid science" exploded. Scientists named this system of receptors and the endocannabinoids that interact with them **the endocannabinoid system**.

How Does the Endocannabinoid System Work?

The endocannabinoid system is made up of the five identified endocannabinoids, the endocannabinoid receptors (two confirmed and a third suspected), and the enzymes that make and break down the endocannabinoids.

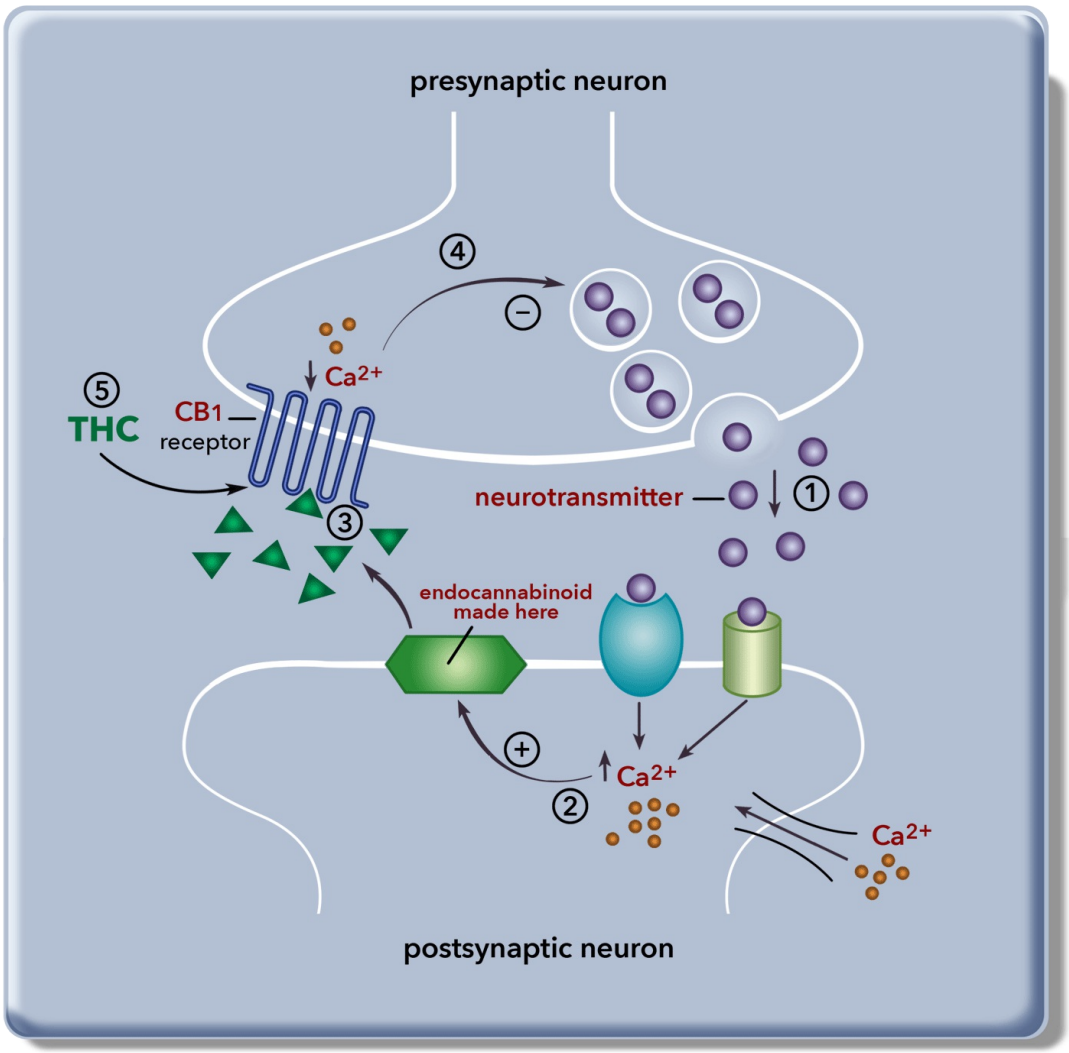


Figure 4: Diagram of endocannabinoid system

This diagram shows two neurons:
the presynaptic neuron that sends the neurotransmitter message
and the postsynaptic neuron that receives the neurotransmitter message

1. When there is too much neurotransmitter being sent by the presynaptic cell, an imbalance occurs causing a disturbance in the postsynaptic cell resulting in…

2. An increase of calcium flowing into the postsynaptic cell, causing the cell to make an endocannabinoid "*key*"

3. The postsynaptic cell then sends the endocannabinoid "*key*" back to bind to the cannabinoid receptor "lock" on the presynaptic cell

4. When the receptor is activated by the endocannabinoid, the presynaptic cell tones down the neurotransmitter message, thereby correcting the imbalance

5. A phytocannabinoid such as **THC** can substitute for an endocannabinoid - both are keys for cannabinoid receptors and can result in a change in the imbalanced neurotransmitter message

Why do we have an Endocannabinoid System?

Very simply, the job of the endocannabinoid system is to regulate the flow of signals that are being sent between cells with *the goal of maintaining balance*, also called homeostasis. It is the way our internal environment responds to changes in the external environment.

Endocannabinoids are made and released by your cells on demand as a response to a trigger. Triggers include injury, illness, inflammation or other imbalances. The endocannabinoid system determines how your cells try to right themselves when something goes wrong and imbalance occurs.

The endocannabinoid system is the most widespread receptor system in the

human body. It regulates many of the most important physiologic pathways in the human body, including:

- gastrointestinal activity
- cardiovascular activity
- pain perception
- modulation of neurotransmitter release
- maintenance of bone mass
- protection of neurons
- hormonal regulation
- metabolism control
- immune function
- inflammatory reactions
- inhibition of tumors cells

As you can see, your endocannabinoid system is involved in just about every chemical process in your body! The Italian researcher Vincenzo Di Marzo, PhD, noted that "the endocannabinoid system is essential to life" and affects how we "relax, eat, sleep, forget and protect."

There is scientific evidence that your endocannabinoid system is "switched on" when you need protection, for instance when certain diseases strike, such as cancer, neuropathic and inflammatory pain, multiple sclerosis, intestinal disorders, post-traumatic stress disorder, traumatic brain injury, hemorrhagic, septic and cardiogenic shock, hypertension, atherosclerosis and Parkinson's disease. In these cases, the endocannabinoids can lessen the negative effects by working to maintain balance of the cells.

You don't feel your pancreas releasing insulin, nor do you know when your thyroid releases thyroid hormone, even though these are essential actions. In much the same way, you don't feel your endocannabinoid system working either, but your brain cells make and use the endocannabinoids to keep the multiple systems in your brain and body functioning correctly, maintaining homeostasis of cell function. **When your endocannabinoid system is not working properly, you may have an imbalance, which can manifest as a medical condition. There are no pharmaceutical medications that directly address an endocannabinoid dysfunction. The cannabis plant is a natural medicine that can help balance the endocannabinoid system for a number of medical conditions.**

Your Endocannabinoid System is Different Than Mine

People who use cannabis can have different experiences despite using the same dose, chemovar or preparation. Other factors such as mindset and the environmental setting can influence response, especially to THC. Why does this happen? **These different responses reflect differences in the baseline endocannabinoid system function of the person who is using cannabis.** If you have a normally functioning endocannabinoid system, you may have a different response to cannabis than someone who has an imbalance in his or her endocannabinoid system.

A great example of this is people who suffer with ADHD. Patients with ADHD have difficulty focusing, completing tasks, organizing tasks and sitting still – all of which makes it hard to succeed at school and at work. We know these patients suffer from an imbalance in a number of their neurotransmitters. Many of my patients with ADHD report that cannabis medicine helps them focus, stay on task, remember things and sit still for a longer period of time. A person using cannabis who doesn't have ADHD may report that cannabis makes them unable to focus or remember things – just the opposite of the ADHD patient. Why is this? The baseline endocannabinoid system in those with ADHD is very different than those without ADHD.

I often tell my patients that I wouldn't prescribe insulin to someone who doesn't suffer with diabetes. The person with diabetes has a poorly functioning pancreas that doesn't produce insulin, which is very different than someone without diabetes. The person with ADHD has an imbalance in neurotransmitters, which is very different than someone without ADHD. In the same way a person with diabetes gets back into balance by taking insulin, a person with ADHD may find balance by taking cannabis medicine as it targets imbalanced neurotransmitters.

Using medicine that targets the non-functioning system should be the goal of all medical treatment. The discovery of the endocannabinoid system and the medical conditions associated with its dysfunction are recognized by the medical community; therefore, we must recognize cannabis as legitimate medicine.

Location of Receptors

The location of the two types of cannabinoid receptors has been mapped out and explains the many diverse effects of cannabis. Certain locations have Type 1 receptors (CB1), some have Type 2 receptors (CB2) and others express both

types of receptors. Also, injury and inflammation can induce certain cells to express Type 2 receptors.

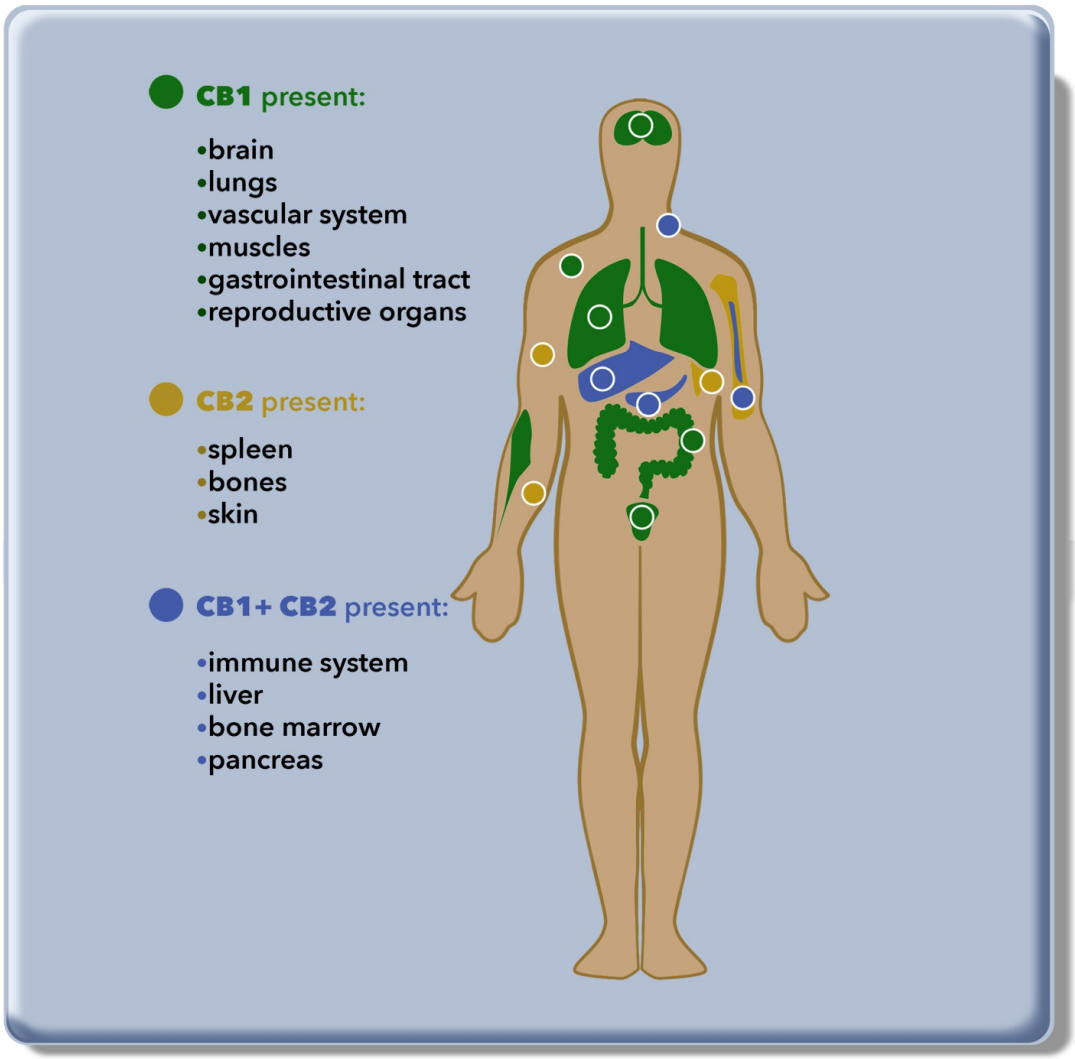


Figure 5: Location of receptors

CB1 receptors are located in areas of brain related to:

- Sensation of Pain (area of brain: amygdala, thalamus, periaqueductal grey matter, also spinal cord)
  - The location of cannabinoid receptors on cells that perceive pain explains why so many patients report pain relief with cannabis use.
  - Some of my patients report that pain disappears completely, some report a dulling of the pain sensation, and some report that pain is unchanged, but they are not focused on it.
- Memory and learning (area of brain: caudate nucleus, hippocampus, putamen)

    - For some patients, such as those with Attention Deficit Disorder, the effects of cannabis can be enhancement of memory and learning.
    - Some of my patients report that with cannabis use they are able to focus and complete a task, retain what they have read, and be more productive and creative at home and at work.
    - For some patients, cannabis interferes with the ability to remember and learn.
- Emotion/Anxiety/Depression/Fear (area of brain: cerebral cortex, limbic system)
    - One of the main conditions I see in my practice is anxiety and/or depression,
    - Cannabis is well known to alleviate anxiety but can in some cases increase it.
    - In my clinical experience, if one has anxiety with cannabis use, it can sometimes be due to a specific chemovar, dosing particulars, or the potency of THC.
- Motor control and coordination (area of brain: cerebellum)
    - Cannabis (THC specifically) has been shown to interfere with motor skills due to cannabinoid receptors located in the cerebellum.
- Appetite (area of brain: hypothalamus)
    - Cannabis (again THC specifically) can increase appetite in some users due to the receptors in the part of the brain that, when triggered, increase appetite; this can be a positive side effect for those who are on chemotherapy or who are underweight; not all cannabis users experience hunger but some patients, especially those who are obese, report it as a negative side effect.
- Nausea/vomiting (area of brain: dorsal vagal complex)
    - Numerous research studies in animals and humans have shown that both THC and CBD act to inhibit nausea and vomiting.
    - Cannabinoid receptors have been found to be particularly abundant in the area of the brain that controls nausea and vomiting.
- Pleasure and reward (area of brain: nucleus accumbens, ventral tegmental area, substantia nigra)
    - THC is known to be euphoric and rewarding as there are cannabinoid receptors in the areas of the brain that regulate gratification and the perception of pleasure.

CB2 receptors are located in areas of body related to:

- Immune system
  - Many immune related cells have these receptors: monocytes, macrophages, B-cells, T-cells, spleen, and tonsils.
  - Type 2 cannabinoid receptors located in the various parts of the immune system have the job of maintaining immunologic homeostasis, meaning these receptors work to keep the immune system balanced.
- Peripheral nervous system
  - Increased levels of Type 2 cannabinoid receptors are found in the nerves of your body after an injury and help decrease the sensation and perception of pain.
- Bone
  - Type 2 cannabinoid receptors are located in bone and have been shown to decrease osteoclast activity (these are the cells that break down bone) and increase osteoblast activity (these are the cells that build up bone).

Areas that express both Type 1 receptors and Type 2 receptors:

- Heart
  - The heart has both Type 1 and Type 2 cannabinoid receptors.
  - The binding of THC to Type 1 receptors in the heart can cause an increased heart rate in new users of cannabis.
  - Type 2 receptors when activated appear to protect the heart from injury (cardioprotective role).
- Liver
  - The human liver can have Type 1 and Type 2 cannabinoid receptors.
  - Binding of a cannabinoid to the Type 1 receptor in an injured or sick liver can cause fibrosis (development of scar tissue).
  - Binding of a cannabinoid to the Type 2 receptor in an injured or sick liver counteracts the progression of fibrosis and works as a protectant.
- Gastrointestinal system
  - Both types of receptors are located in the nervous system of the gut

called the enteric nervous system, where they inhibit gastric secretions, decrease gut inflammation and pain, and reduce gastric motility.

- Reproductive System
  - Cannabinoid receptors in the female reproductive organs regulate fertility, maternal/fetal signaling, development of the placenta and embryo.
  - Cannabinoid receptors in the male reproductive organs regulate Sertoli Cell survival, spermatogenesis, sperm-oocyte interaction and the blockade of polyspermy.
- Skin
  - Both types of receptors have been found in the skin, specifically keratinocytes, and the epithelial cells of hair follicles, sebocytes and eccrine sweat glands. They are also found in the nerve fibers of the skin.
  - These receptors are thought to mediate anti-inflammatory and pain sensation in the skin.

No Risk of Fatal Phytocannabinoid Overdose due to Receptor Location

There are no cannabinoid receptors in the area of the brain that controls breathing and heart rate. This explains why there is no possibility of a fatal overdose with phytocannabinoids. In contrast, there is an abundance of opioid receptors in the respiratory control center in the brain. When high doses of opioid compounds, such as heroin, methadone or oxycodone, bind to opioid receptors in the respiratory control center of the brain, the respiratory drive can be suppressed and can lead to respiratory arrest. This is not an issue with the cannabinoids found in cannabis.

Additional Endocannabinoid Targets

Endocannabinoids have been found to bind to non-cannabinoid receptors and also to activate certain proteins in addition to cannabinoid receptors. These targets include:

- GPR55 receptor, which regulates pain and production of endocannabinoids
- TPRV family of protein ion channels, which are involved in

inflammation and pain response

- PPARS, receptors that regulate translation of genes involved in metabolism and energy homeostasis, and also confer cardioprotection and neuroprotection

Endocannabinoid System Dysfunction

Dysfunction of the endocannabinoid system is like the proverbial chicken and egg. The dysfunction can be a result of chronic medical conditions or can cause chronic medical conditions. When the endocannabinoid system is functioning well, homeostasis of many of the brain and body's physiologic processes are maintained. Underactivity or overactivity of the endocannabinoid system has been linked to disease states and is the focus of much research throughout the world. Understanding how the dysfunction of the endocannabinoid system can cause disease or can result from disease is crucial to its use as a medicinal compound.

Endocannabinoid Deficiency Syndrome

In 2003, Dr Ethan Russo, a board-certified neurologist and psychopharmacology researcher, posed an excellent question in a scientific paper, asking if a deficiency of endocannabinoids – the compounds that are made on demand in our brains and bodies to maintain homeostasis – can lead to disease. He hypothesized that having lower levels of these compounds, which would diminish the ability to maintain homeostasis, may lead to medical conditions such as migraine headaches, fibromyalgia, irritable bowel syndrome and other "treatment-resistant" conditions. He reported that many patients with these conditions who used cannabis medicine had improvement of their symptoms.

Since that article was published, there have been numerous scientific studies that demonstrate that an impairment or dysfunction of the endocannabinoid system can be the cause of significant and difficult to treat medical conditions. This deficiency may be genetically determined, meaning you are born with it, while others may develop it later in life. Chronic stress, poor diet, and chronic pain have all been shown to negatively impact endocannabinoid system functioning and can lead to endocannabinoid dysfunction.

Medical conditions that have been shown to result from endocannabinoid system dysfunction include:

- Autoimmune diseases
- Epilepsy

- Migraine headaches
- Fibromyalgia/Myofascial Pain Syndrome
- Irritable Bowel Syndrome
- Failure to Thrive in newborns
- Complex Regional Pain Syndrome
- Cardiovascular disease
- Anxiety and Depression
- Schizophrenia
- Multiple Sclerosis
- Nausea and Motion Sickness
- Huntington's disease
- Parkinson's disease
- Menstrual symptoms

Endocannabinoid Overactivity

In addition to an endocannabinoid deficiency, there can be dysregulation of the endocannabinoid system at the other end of the spectrum, namely overactivity. One example is the role of the ECS in appetite, food intake, and energy metabolism.

Researcher Dr. Vincenzo Di Marzo reported in 2008 that overactivity of the ECS may be associated with obesity and Type 2 diabetes. Early research shows that people who are overweight/obese and those with Type 2 diabetes have abnormally elevated blood levels of endocannabinoids. The elevation of endocannabinoid levels may be due to lower levels of the enzymes that are needed to break down the endocannabinoids. Preliminary studies show that overweight/obese people do not make enough of these enzymes, resulting in the endocannabinoids hanging around longer at the receptor, and continuing to activate them. This results in increased hunger, which increases weight, which then increases endocannabinoid levels, which then increases hunger and so on, creating a vicious cycle of endocannabinoid dysfunction.

When obese men who had elevated endocannabinoid levels were enrolled for one year in a lifestyle modification program requiring healthy eating and physical activity, their abnormally elevated endocannabinoid levels decreased, weight and waist circumference was reduced, triglyceride levels decreased and

healthy cholesterol levels increased. More research is needed, but it appears that maintaining normal weight with healthy diet and exercise helps to keep the

endocannabinoid system functioning normally.

The Story of Rimonabant

Rimonabant is a synthetic drug that works as a Type 1 cannabinoid receptor inverse agonist, which means it binds to the receptor but causes the opposite effect. Rimonabant, by causing the opposite effect of endocannabinoids and THC at the CB1 receptor, blocks hunger and has an effect on energy metabolism. It was tested in placebo-controlled studies in thousands of overweight or obese patients, some with diabetes, high cholesterol, low HDL and triglycerides (TGL), and was found to have numerous benefits, including sustained weight loss, reduction of TGL, increase in HDL and better blood glucose control. Unfortunately, this drug also caused a number of significant and unacceptable side effects, including depression, suicidal ideation, nausea, anxiety and dizziness. Although Rimonabant was available in Europe starting in 2006, it was removed from the market in 2008 as its risks clearly outweighed its benefits. Pharmaceutical companies are still investigating synthetic compounds that block the CB1 receptor as treatments for obesity and Type 2 diabetes.

Cannabinoid Receptors Up-regulation and Down-regulation

Cannabinoid receptors can change in number in response to what is going on around them in the brain and body. Scientists call the increase in number of cannabinoid receptors "up-regulation" and the decrease in the number of cannabinoid receptors "down-regulation."

Research has shown that some disease states are associated with up-regulation of receptors.

- Animals that have seizures have shown an increase in cannabinoid receptors in certain parts of their brains.
- Animals that have Crohn's colitis-type illness have been found to have extra cannabinoid receptors in their intestines.
- Animals that suffer with nerve pain show an up-regulation of cannabinoid receptors in certain parts of their brains.
- Animals that are sleep deprived show an increase in cannabinoid receptors in their brains.
- Autistic children have been found to have increased number of Type 2 cannabinoid receptors on their white blood cells (autism often includes an element of immune dysfunction).

- Cannabinoid receptors were found to be up-regulated in persons that had depression who committed suicide.

One theory is the increase in the cannabinoid receptors may be a compensatory or protective mechanism: you have more receptors because your cells are looking for endocannabinoids to help restore balance. Up-regulation has also been found to be maladaptive in some instances, such as increasing cellular fat deposits in liver disease.

Cannabinoid receptors can also down-regulate, that is, there are *less* receptors available for cannabinoid binding. What happens is that the cannabinoid receptors, usually in the case of being overactivated, will move from their location on the cell wall and "hide" inside the cell itself. Again, this is thought to be a protective mechanism.

We see that chronic heavy users of THC-rich cannabis have a decrease in the number of cannabinoid receptors. This down-regulation explains how chronic heavy users develop tolerance to the effects of cannabis. Tolerance is also regionally selective, meaning that different parts of the brain can develop tolerance while other parts of the brain may not. For example, one of my patients who started using cannabis for multiple sclerosis found excellent relief of her spasticity from THC-rich cannabis. Initially, she experienced some memory loss, but found that after a few months of use, this effect was no longer an issue. During this time, she never lost the beneficial effect on the spasticity.

Using THC-rich cannabis (especially high potency THC) daily for months will likely result in lower numbers of cannabinoid receptors, creating tolerance to the effects. At this point the patient has to increase the amount or potency of THC in order to get the same effect. Although this is not dangerous, loss of the medical effect and the higher financial cost of using more and higher potency cannabis is not ideal.

By abstaining from cannabis use, the receptors will become available again and tolerance will lessen. Studies show that abstention from cannabis use for approximately 28 days results in a return of normal numbers of cannabinoid receptors. However, for medical patients that rely on cannabis medicine for their chronic conditions, abstaining for this length of time may not be possible as quality of life may be negatively impacted.

I recommend using the lowest dose that gives the desired effects. By starting low dose and increasing to therapeutic effects, one can usually avoid tolerance. However, if there is loss of beneficial effects, taking regular breaks from using THC-rich products is helpful in maintaining receptor availability. Taking one or two days off per week or one week off every 2-3 months will minimize the down-regulation of cannabinoid receptors and the response to the medical effects of THC can be maintained.

It's Not a Miracle, It's Science

Many of my patients who were suffering prior to cannabis treatment recollect feeling quite desperate by the time they came to see me. Trying different therapies, sometimes for years without any improvement in quality of life, can change a person profoundly, causing depression, anxiety and a sense of hopelessness. After finding relief with cannabis, many think it is a miracle, and it can certainly feel that way.

It is *not* a miracle, it is science. If your endocannabinoid system is not functioning well, simply put, you are out of balance. If dysfunction of the endocannabinoid system is the culprit, prescribed medications do not target this system and relief is not achieved. Chronic illness leads to chronic stress, which negatively impacts the endocannabinoid system, keeping it out of balance.

For many patients, using cannabis targets the cause of the medical condition, the endocannabinoid system, and healing can begin. For some the effects are immediate, and for others it may take time for the system to get back into balance.

Studies show that once the ECS is functioning well, less cannabis can be used to maintain homeostasis. Commonly, patients report that when they initially started using cannabis, they were using higher doses and, after a few months, their dosing requirements went down. It may take time to achieve this if you have been sick and under stress for a long time. Using other natural modalities that have shown to help the endocannabinoid system stay balanced, such as a healthy diet, regular exercise, mindful stress reduction techniques, such as meditation, tai-chi, and yoga, in addition to cannabis as medicine, can be the solution.

Sources

Bensaid M, Gary-bobo M, Esclangon A et al.: The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol. Pharmacol. 63, 908-914 (2003).

Cabral GA, Griffin-Thomas L. Emerging Role of the CB_2 Cannabinoid Receptor in Immune Regulation and Therapeutic Prospects. Expert reviews in molecular medicine 2009;11:e3. doi:10.1017/S1462399409000957.

Choukèr, Alexander, et al. "Motion sickness, stress and the endocannabinoid system." PLoS One 5.5 (2010): e10752.

D'Argenio, Giuseppe, et al. "Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation." The FASEB journal 20.3 (2006): 568-570.

Devane, William A., et al. "Determination and characterization of a cannabinoid receptor in rat brain." Molecular pharmacology 34.5 (1988): 605-613.

Devane, William A., et al. "Isolation and structure of a brain constituent that binds to the cannabinoid receptor." Science 258.5090 (1992): 1946-1949.

Di FM, Pini LA, Pelliccioli GP, Calabresi P, Sarchielli P (2008) Abnormalities in the cerebrospinal fluid levels of endocannabinoids in multiple sclerosis. J Neurol Neurosurg Psychiatry 79: 1224–1229

Di Marzo, Vincenzo, and Isabel Matias. "Endocannabinoid control of food intake and energy balance." Nature neuroscience 8.5 (2005): 585-589.

Di Marzo, V., et al. "Changes in plasma endocannabinoid levels in viscerally obese men following a 1 year lifestyle modification programme and waist circumference reduction: associations with changes in metabolic risk factors." Diabetologia 52.2 (2009): 213-217.

Di Marzo, V. "The endocannabinoid system in obesity and type 2 diabetes." Diabetologia 51.8 (2008): 1356-1367.

Di Marzo, V., et al. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends in Neuroscience (1998) 21: 521–528.

Duncan, M., J. S. Davison, and K. A. Sharkey. "Review article: endocannabinoids and their receptors in the enteric nervous system." Alimentary pharmacology & therapeutics 22.8 (2005): 667-683.

Dunnett, Alenka J., et al. "The diagnosis of fibromyalgia in women may be influenced by menstrual cycle phase." Journal of Bodywork and Movement Therapies 11.2 (2007): 99-105.

Ferguson, G., and M. A. Ware. "Review Article: Sleep, Pain and Cannabis." Journal of Sleep Disorders & Therapy 2015 (2015).

Fride, Ester, Tatyana Bregman, and Tim C. Kirkham. "Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood." Experimental Biology and Medicine 230.4 (2005): 225-234.

Gaoni, Yechiel, and Raphael Mechoulam. "Isolation, structure, and partial synthesis of an active constituent of hashish." Journal of the American Chemical Society 86.8 (1964): 1646-1647.

Hajrasouliha, Amir Reza, et al. "Endogenous cannabinoids contribute to remote ischemic preconditioning via cannabinoid CB 2 receptors in the rat heart." European journal of pharmacology 579.1 (2008): 246-252.

Herkenham, M., et al, Cannabinoid Receptor Localization in Brain. Proceedings of the National Academy of Sciences USA 87 (1990): 1932-36

Hill MN, Miller GE, Carrier EJ, Gorzalka BB, Hillard CJ (2009) Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. Psychoneuroendocrinology 34: 1257–1268

Hill, M. N., and B. B. Gorzalka. "Is there a role for the endocannabinoid system in the etiology and

treatment of melancholic depression?." Behavioural pharmacology 16.5-6 (2005): 333-352.

Hirvonen, J., et al. "Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers." Molecular psychiatry 17.6 (2012): 642-649.

Hungund, B. L., et al. "Upregulation of CB1 receptors and agonist-stimulated (^{35}S)GTPγS binding in the prefrontal cortex of depressed suicide victims." *Molecular psychiatry* 9.2 (2004): 184-190.

Kathuria, Satish, et al. "Modulation of anxiety through blockade of anandamide hydrolysis." Nature medicine 9.1 (2003): 76-81.

Kaufmann, I., et al. "Enhanced anandamide plasma levels in patients with complex regional pain syndrome following traumatic injury: a preliminary report." European Surgical Research 43.4 (2009): 325-329.

Koethe, Dagmar, et al. "Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis." The British Journal of Psychiatry 194.4 (2009): 371-372.

Ludányi, Anikó, et al. "Downregulation of the CB1 cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus." The Journal of neuroscience 28.12 (2008): 2976-2990.

Maccarrone, M. "CB2 receptors in reproduction." British journal of pharmacology 153.2 (2008): 189-198.

Manzanares, J., et al. "Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes." Current neuropharmacology 4.3 (2006): 239-257.

Matias, Isabel, et al. "Regulation, function, and dysregulation of endocannabinoids in models of adipose and β-pancreatic cells and in obesity and hyperglycemia." *The Journal of Clinical Endocrinology & Metabolism* 91.8 (2006): 3171-3180.

Mechoulam, Raphael, et al. "Early phytocannabinoid chemistry to endocannabinoids and beyond." Nature Reviews Neuroscience (2014).

Miller, Lydia K., and Lakshmi A. Devi. "The highs and lows of cannabinoid receptor expression in disease: mechanisms and their therapeutic implications." Pharmacological reviews 63.3 (2011): 461-470.

Monory, Krisztina, and Beat Lutz. "The endocannabinoid system as a therapeutic target in epilepsy." Cannabinoids and the Brain. Springer US, 2008. 407-422.

Monteleone, Palmiero, et al. "Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa." Neuropsychopharmacology 30.6 (2005): 1216-1221.

Pacher P, Steffens S (2009) The emerging role of the endocannabinoid system in cardiovascular disease. Semin Immunopathol 31: 63–77

Park, Jae Myung, et al. "Cannabinoid receptor 1 gene polymorphism and irritable bowel syndrome in the Korean population: a hypothesis-generating study." Journal of clinical gastroenterology 45.1 (2011): 45-49.

Pertwee, Roger G. "Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities." Philosophical Transactions of the Royal Society B: Biological Sciences 367.1607 (2012): 3353-3363.

Richardson, Jennelle Durnett, Lin Aanonsen, and Kenneth M. Hargreaves. "SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice." European journal of pharmacology 319.2 (1997): R3-R4.

Russo, Ethan B. "Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?" Neuroendocrinol Lett 25 2004 (1-2):31-39.

Russo, Ethan B. "Clinical endocannabinoid deficiency reconsidered: Current research supports the

theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes." Cannabis and Cannabinoid Research (2016b) 1:154-165.

Sam, Amir H., Victoria Salem, and Mohammad A. Ghatei. "Rimonabant: from RIO to ban." Journal of obesity (2011).

Schwarz E, Whitfield P, Nahnsen S, Wang L, Major H, et al. Alterations of primary fatty acid amides in serum of patients with severe mental illness. Frontiers in Bioscience (2011) 3: 308–314.

Siegling, Angela, et al. "Cannabinoid CB< sub> 1</sub> receptor upregulation in a rat model of chronic neuropathic pain." European journal of pharmacology 415.1 (2001): R5-R7.

Siniscalco, Dario, et al. "Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders." Journal of autism and developmental disorders 43.11 (2013): 2686-2695.

Sipe, Jack C., et al. "Reduced endocannabinoid immune modulation by a common cannabinoid 2 (CB2) receptor gene polymorphism: possible risk for autoimmune disorders." Journal of leukocyte biology 78.1 (2005): 231-238.

Smith, Steele Clarke, and Mark S. Wagner. "Clinical endocannabinoid deficiency (CECD) revisited." Neuroendocrinology Letters 35.3 (2014).

Ständer, Sonja, et al. "Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin." Journal of dermatological science 38.3 (2005): 177-188.

Storr, Martin A., et al. "Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis." Inflammatory bowel diseases 15.11 (2009): 1678-1685

Storr, M. A., et al. "The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome." Neurogastroenterology & Motility 20.8 (2008): 857-868.

Sugiura, Takayuki, et al. "2-Arachidonoylgylcerol: a possible endogenous cannabinoid receptor ligand in brain." Biochemical and biophysical research communications 215.1 (1995): 89-97.

Volfe, Z., A. Dvilansky, and I. Nathan. "Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients." International journal of clinical pharmacology research 5.4 (1984): 243-246.

Wallace, Melisa J., et al. "The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy." Journal of Pharmacology and Experimental Therapeutics 307.1 (2003): 129-137.

Wang L, Yang T, Qian W, Hou X (January 2011). "The role of endocannabinoids in visceral hyposensitivity induced by rapid eye movement sleep deprivation in rats: regional differences". Int. J. Mol. Med. 27 (1): 119–26.

Sophie's Story

I went to medical school from 1986 to 1990 and did an internship from 1990-1993, completely unaware of the incredible discoveries of the cannabinoid receptor and the endocannabinoid system. By 1995, the first two endocannabinoids were discovered, but cannabis medicine was still unknown to most physicians.

When three-month-old Sophie was diagnosed with infantile spasms, a rare seizure disorder with a particularly grim prognosis, in June of that year, the neurologists began a course of high dosage steroids and benzodiazepines. By the time she was nine months old, Sophie's development had plateaued, she was on three anti-epileptic medications and the seizures kept coming. The neurologists in New York City could find no reason for her epilepsy and diagnosed her with cryptogenic infantile spasms. Over the next 19 years, Sophie was treated with 22 drugs and two courses of the ketogenic diet, along with countless alternative therapies, including osteopathy, Chinese herbs and acupuncture. Her spasms evolved into mixed seizures but no medication helped stop them. She suffered from serious side effects, and her quality of life was sometimes unbearable.

Sophie's mother Elizabeth told me that her old life ended on the day Sophie was diagnosed and her new life began on that day: a life of sleepless nights and days filled with intense caregiving, witnessing the constant suffering of her daughter, and navigating all the systems of care that having a sick and disabled child demanded. Sophie is severely disabled as a result of the seizures and the medications. While she can walk, she needs complete assistance with all life tasks, including feeding and diapering. She is non-verbal and needs a wheelchair because she tires easily and has seizures unexpectedly. She has hurt herself countless times, knocked out permanent teeth, gotten stitches, broken her leg and hand and nose, as well as suffered contusions and scrapes.

Even as her mother became a nationally recognized advocate for children with special healthcare needs, she never gave up hope that there was something that might help her daughter and, as the years went by, she became more and more convinced the traditional treatments for refractory epilepsy were nothing but a crapshoot. When she started hearing about cannabis and its effects on seizures, she began to explore the cannabis laws in California and eventually found her way to a well-trusted cannabis provider.

In December of 2013, Sophie was one of my first patients to get tested quality CBD-rich oil. Within two weeks of starting the oil, Sophie had the first seizure-free day of her life, followed by a period of several weeks with no seizures. She began to smile and appeared relaxed and comfortable for the first time in decades.

It's been two years since Sophie first began taking cannabis and, while not seizure-free, she has at least 90% fewer seizures and those she does have are shorter and less intense. Sophie recovers from them more quickly and hasn't needed a rescue medication since she began taking cannabis. Her mother reports that they are slowly weaning Sophie off of the two medications she's been on for eight years, and while withdrawal is difficult, the cannabis and added THC-rich oil has lessened those symptoms.

I think often about the birth of and then early diagnosis of Sophie – how her life and treatment virtually coincided with our initial forays into researching and learning about the endocannabinoid system. Elizabeth doesn't waste time thinking what Sophie's life and the life of her family might have been if they had been able to try cannabis back when she was a baby and first diagnosed.

While she shared with me how angry she feels when she's contacted by parents of young children on four and five medications yet still seizing, she is encouraged that more and more families in the epilepsy community are seeing the effects of cannabis medicine and fighting for access to it. She is at peace knowing Sophie's quality of life is now dramatically better and that her whole family rests easier.

CHAPTER 3
Safety Profile of Cannabis

In August 2015 the acting chief of the Drug Enforcement Agency said, "If you want me to say that marijuana's not dangerous, I'm not going to say that because I think it is. Do I think it's as dangerous as heroin? Probably not. I'm not an expert." Three months later, he said in a briefing to reporters, "What really bothers me is the notion that marijuana is also medicinal – because it's not. We can have an intellectually honest debate about whether we should legalize something that is bad and dangerous, but don't call it medicine – that is a joke." He went on to say, "There are pieces of marijuana – extracts or constituents or component parts – that have great promise, but if you talk about smoking the leaf of marijuana – which is what people are talking about when they talk about medicinal marijuana – it has never been shown to be safe or effective as a medicine."

Political posturing aside, the chief of the DEA has probably never heard of the endocannabinoid system.

Despite the lies, political agendas and propaganda, science clearly shows that cannabis is one of the safest substances known to man. Over the past hundred plus years, numerous large investigations into the safety of cannabis have been published. Here are some highlights:

- 1894: The Indian Hemp Drugs Commission Report was an Indo-British study of cannabis usage in India. The Commission researched cannabis use for two years and wrote a report over 3,000 pages long, concluding that, "moderate use of hemp drugs appears to cause no appreciable physical injury of any kind, moderate use of these drugs produces no mental injury, and moderate use produces no moral injury whatever."
- 1944: New York City Mayor Fiorello LaGuardia, angered by the passage of the 1937 Marijuana Tax Act, commissioned the New York Academy of Science to research claims made by the Federal government that smoking cannabis "results in insanity, deteriorates physical and mental health, assists in criminal behavior and juvenile delinquency, is physically addictive and is a 'gateway' drug to more dangerous drugs." After five years of research, the report systematically disproved each claim.
- 1972: The National Commission on Marijuana and Drug Abuse was created as part of the Controlled Substance Act to research cannabis abuse in the US. The final report entitled "Marihuana, A Signal of

Misunderstanding," was presented to Congress and the public recommended ending marijuana prohibition. The report noted, "there is little proven danger of physical or psychological harm from the experimental or intermittent use of the natural preparations of cannabis" and went on to say, "the use of drugs for pleasure or other non-medical purposes is not inherently irresponsible; alcohol is widely used as an acceptable part of social activities." The Nixon administration ignored the findings of the Commission and designated cannabis as a Schedule I Controlled Substance, the most restrictive category defining these compounds as having no medicinal value, high potential for abuse and high potential for addiction.

- 1988: Fourteen years after the National Organization for Reform of Marijuana Laws (NORML) filed a petition with the DEA to reschedule cannabis from a Schedule I controlled substance to a Schedule II controlled substance which would allow doctors to prescribe it and researchers to study it, US Drug Enforcement Administration (DEA) Chief Administrative Law Judge Francis Young wrote in his ruling that, "Marijuana, in its natural form, is one of the safest therapeutically active substances known to man. By any measure of rational analysis marijuana can be safely used within a supervised routine of medical care." He also wrote, "it would be unreasonable, arbitrary and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record." He stated that there was no evidence of lack of accepted safety with medical supervision and he recommended rescheduling it. However a DEA administrator named John Lawn rejected the recommendation and a 1994 Court of Appeals sided with the rejection, leaving cannabis as a Schedule I substance.
- 2015: The U.S Surgeon General Dr. Vivek Murthy stated that, "We have some preliminary data that for certain medical conditions and symptoms, that marijuana can be helpful," and goes on to say that he believes U.S. marijuana policy should be driven by science, saying, "we have to use that data to drive policy-making."
- August 2016: The DEA denies the fourth petition to reschedule cannabis, however the acting DEA administrator admitted, "marijuana is less dangerous than some substances in other schedules."

No lethal dose has ever been reported, nor is it even known what a lethal dose of THC might be in humans. The LD-50 (LD = lethal dose) of THC has been investigated. The LD-50 of a drug is the dose at which 50% of those taking the drug would die; it is expressed in how many mg of the drug would need to be consumed per kg of body weight. Laboratory animals such as rats,

mice, dogs and monkeys can tolerate up to 1000mg/kg of THC. This is equal to a 150 pound adult human taking 70,000mg of THC or about 5,000 times the dose people use to get the desired effects (10-20mg).[1] What this means is that there is no LD-50 for cannabis!

The Centers for Disease Control (CDC) compiles yearly mortality data that show deaths from alcohol, tobacco, and other substances. The latest CDC data report that in the US in 2010, there were 25,692 alcohol-related deaths (excluding deaths from indirect causes such as unintentional injury, homicide and fetal alcohol syndrome)[2] and 440,000 tobacco-related deaths.[3] Overdoses and other related drug use with prescription drugs (mainly painkillers and anti-anxiety drugs) caused 37,792 human deaths, accounting for more fatal overdoses than heroin and cocaine combined.[4] In 2015, the CDC reported that 44 people die every day in the US from prescription opiate overdose.[5]

During the years 2000-2004, an estimated 3 million people in Great Britain used cannabis. No deaths from cannabis were reported during that period. During the same time period, heroin or other opiate overdoses caused 1,000 deaths, and alcohol-related deaths numbered more than 100,000, as did tobacco.[6]

The CDC no longer has a category for cannabis deaths, as there are no reported deaths.

There have been numerous animal studies investigating the toxic effects of cannabis on the brain and other organs of the body. However, researchers have not been able to reproduce early animal studies that reported brain or organ damage. In many studies, very large doses of cannabis were given to the subjects in order to produce significant damage and the ability to correlate these findings to doses used by human cannabis users is challenging. Overall, the available animal data shows little evidence of brain or other organ damage. As you learned in the previous chapter, there are no fatal overdoses of cannabis because the area of the brain responsible for breathing and heart rate does not have cannabinoid receptors.

As to whether effects of long-term exposure to cannabis causes persistent cognitive deficits in adults, the tremendous methodological difficulties inherent in this type of study is obvious as the many variables would be very difficult to control. One study that attempted this investigation recruited 63 current heavy cannabis users and 72 control subjects. Subjects underwent a 28-day washout from cannabis, called the abstinence period. On days 0, 1, and 7 of abstinence, the heavy users scored significantly below control subjects on a battery of neuropsychological tests. By day 28 there were virtually no differences between the groups on any of the test results.[7]

There has been some concern about cannabis causing schizophrenia. It

appears from studies that when the adolescent brain is exposed to chronic heavy use of THC-rich cannabis, the endocannabinoid system is disturbed enough to interfere with the development of the brain, especially the maturation of prefrontal circuitry. The adolescent with a genetic predisposition for schizophrenia (i.e., a family member with mental illness such as schizophrenia or bipolar disorder) appears to be most vulnerable. Once the brain is fully developed, studies show there is no increased risk of schizophrenia with cannabis use.

There is some research that shows that teenagers between the ages of 13 and 18 are most vulnerable to problems resulting from regular cannabis use as this particular time is when significant brain development, such as higher-order thinking and executive functioning, is taking place.[8,9] A balanced and functioning endocannabinoid system is crucial for this brain development to take place, and the use of THC can interfere with this process.[10,11,12] In general, unless there is a significant medical condition where the benefits of medicinal cannabis outweigh the risks, cannabis use, specifically THC, should be avoided in anyone whose brain is still developing.

Sources

[←1]

Iversen, L., The Science of Marijuana. Oxford University Press 2008

[←2]

Murphy, S., National Vital Statistic Reports. Deaths: Final Data for 2010, Volume 61, Number 4, May 2013

[←3]

Centers for Disease Control and Prevention. Smoking and Tobacco Use, Tobacco-Related Mortality. www.cdc.gov

[←4]

Centers for Disease Control and Prevention. CDC Newsroom. "Opioids dive continued increase in drug overdose deaths." www.cdc.gov

[←5]

Centers for Disease Control and Prevention. National Vital Statistics System mortality data. (2015)

[←6]

Advisory Council on Misuse of Drugs, 2006

[←7]

Pope H., Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry* (2001) 58: 909-91.

[←8]

Silins, Edmund, et al. "Young adult sequelae of adolescent cannabis use: an integrative analysis." *The Lancet Psychiatry* 1.4 (2014): 286-293.

[←9]

Jacobus, Joanna, and Susan F Tapert. "Effects of Cannabis on the Adolescent Brain." *Current pharmaceutical design* 20.13 (2014): 2186-2193.

[←10]

Bossong, Matthijs G., and Raymond JM Niesink. "Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia." *Progress in neurobiology* 92.3 (2010): 370-385.

[←11]

De Hert, Marc, et al. "Effects of cannabis use on age at onset in schizophrenia and bipolar disorder." *Schizophrenia research* 126.1 (2011): 270-276.

[←12]

Casadio, Paola, et al. "Cannabis use in young people: the risk for schizophrenia." *Neuroscience & Biobehavioral Reviews* 35.8 (2011): 1779-1787.

CHAPTER 4
How to Use Cannabis as Medicine

In order to use cannabis as medicine successfully, there are a number of concepts that you should understand. These include:

1. Effects of THC
2. Effects of CBD
3. Other cannabinoids: CBN, THCA, CBDA, THCV, CBDV
4. How to understand cannabis testing results
5. Different methods of using cannabis: inhalation/ingestion/sublingual/transdermal/rectal/topical
6. Advantages and disadvantages of the different ways to take cannabis
7. CBD: THC ratio and concentration
8. How to understand cannabis product labels
9. How to dose cannabis
10. First time use
11. Overdosing on cannabis
12. Medicinal versus recreational use
13. Comparison of the most common delivery methods

Effects of THC

THC is the most prominent cannabinoid in the cannabis plant and is responsible for the psychoactive "high" effects. Many think THC is just for getting high, but it is quite medicinal in its effects for thousands of patients. The claim that THC is recreational only and has no medicinal value is bogus.

I often read in medical journals that psychoactive effects are "unwanted," and although that may be true for some people, many of my patients report significant and life-changing relief with THC-rich cannabis. This does not make these patients "potheads." Remember that people with chronic and

serious illnesses often suffer with endocannabinoid deficiency or dysregulation, meaning their endocannabinoid system is not working properly. **THC can and does correct this imbalance for many patients.** A person with an endocannabinoid dysfunction who finds THC-rich cannabis to be helpful should have access to this medicine, just as someone with diabetes or asthma should have access to the medications that benefit them. After talking with thousands of patients who have found excellent results with THC-rich cannabis medicine, I can definitively state that it is a safe and effective medication when used responsibly. As with all medicines, there are a few circumstances where THC use should be avoided (see Chapter 5).

THC works directly by binding to the cannabinoid receptor similarly to the way endocannabinoids bind to these receptors. Remember that your endocannabinoid system works to maintain homeostasis of your cells. When there is a trigger such as illness, injury or inflammation, if your endocannabinoid system functions properly, you will make endocannabinoids that will balance the cells' messages. As discussed in Chapter 3, certain medical conditions are associated with an endocannabinoid deficiency and those suffering with this deficiency cannot respond to cellular imbalance as they do not have enough endocannabinoids to respond to the trigger. THC can replace the missing endocannabinoids and natural balance can be restored.

A good example of this is neuropathic pain, also called neuropathy, a painful condition that is notoriously difficult to treat with conventional pharmaceuticals. In neuropathy, often associated with diabetes, HIV/AIDS, multiple sclerosis or chemotherapy toxicity, an excitatory neurotransmitter called glutamate can accumulate and cause cell damage and death, worsening the pain. We know endocannabinoids are released in response to these insults, but sometimes these compounds cannot fully correct the imbalance, especially in cases of endocannabinoid deficiency. THC, which binds to the cannabinoid receptor, decreases the transmission of glutamate, resulting in cellular protection and diminished pain.

In my clinical experience, THC-rich cannabis medicine is used for chronic pain, anxiety, depression, insomnia, appetite stimulation, gastrointestinal ailments and nausea and vomiting, especially when induced by chemotherapy. Studies prove that THC works as a neuroprotectant and as an anti-inflammatory, anticonvulsant, antispasmodic, antitumor and antioxidant agent. Some patients have such significant relief of their conditions, especially arthritis, insomnia, intestinal distress and migraine headaches, that they think they are cured. They also often find that once they are improved, low and intermittent doses of cannabis keep their conditions under control. Some patients will feel so well that they will stop using cannabis completely and may find that the medical condition does not return. Others find that continued use of cannabis maintains balance and that the medical condition is managed

easily.

One particular patient came to me with a long history of migraine headaches that started when he was a young teenager. His mother, grandmother and three siblings all suffered with migraines as well. He had complete resolution of his migraines for one year with the use of THC-rich cannabis. Thinking he was cured and no longer needed treatment, he stopped using it. Three months later he came back to see me, reporting that the migraines had returned. He resumed his use of cannabis medicine and remains migraine free. He reports that low doses of vaporized THC a few nights per week keep the headaches away, with the beneficial side effects of less anxiety, better sleep and no adverse side effects. This patient likely suffers from a genetic endocannabinoid deficiency that causes his migraine condition. The use of THC allows his brain to maintain balanced neurotransmitter messages, resulting in resolution of his condition.

Potency of the cannabis plant is usually measured by the content of THC, which can range from 5% up to 30%. Concentrated forms of THC-rich cannabis can have potencies up to 90%. The average potency of cannabis in the 1970s was 1-3% and now ranges between 10-20% in states with medical cannabis laws. I have not seen issues with this increase as patients using cannabis for medical purposes rarely over-medicate. They use trial and error to find the dose that alleviates the medical condition, and if they use more, they find that the higher dose can be uncomfortable or with the development of tolerance over time, the beneficial medicinal effects may be lessened or lost. Most of my patients using THC-rich cannabis report that they don't need much to get the results they are seeking. When a patient reports using large amounts of THC, tolerance has usually developed. **Abstaining for a few days to a week will diminish the tolerance and allow the patient to lessen the amount of cannabis being used while likely improving the medicinal effects.**

There are a few things to keep in mind when using THC-rich cannabis medicine:

- Different people respond differently to THC – some people feel significant effects and some do not.
- Patients should use the lowest dose that gives the desired effects so that tolerance can be limited.
- Daily users of THC who experience a loss of medicinal effects should take breaks, either skipping use 1-2 days per week or 1 week every few months to allow the number of cannabinoid receptors to remain as close to normal as possible.
- Patients should make sure to keep THC-rich cannabis medicine away

from children and pets.

- The most common side effects from THC-rich cannabis are dry mouth, feeling lightheaded or dizzy, rapid heartbeat, reddening of the eyes, coughing from inhalation of smoke or vapor; although not dangerous, new patients may feel anxious or even panic with a sense of perceived harm.

Effects of CBD

Cannabidiol is the second most prominent cannabinoid in the plant. As research into the amazing medicinal properties of CBD continues to increase, more CBD chemovars and products are becoming available and more medical cannabis patients are including CBD in their regimens. Whereas THC binds directly to the cannabinoid receptor, CBD does not bind directly to the receptors. Recently CBD was found to be an allosteric modulator of the receptor, meaning it influences the compounds that bind to the receptor. It also works at multiple other targets. These include non-cannabinoid receptors and ion channels where calcium, potassium and sodium pass in and out of cells. **This is why CBD has no psychoactive effects and does not cause tolerance with repeated use.** CBD is well documented to be extremely safe for human use. CBD is often alerting in low to moderate doses and can be sedating in higher doses. Occasionally, new CBD users may experience sedation initially, which usually resolves in the first few weeks of use.

CBD has multiple properties and can act as an anti-inflammatory, antioxidant, anticonvulsant, antianxiety, antidepressant, anti-psychotic, antibacterial and antitumor agent. It also works as a pain reliever and muscle-relaxant. Research shows that the brain's endocannabinoid activity is enhanced by CBD, as CBD blocks the breakdown of these compounds, allowing them to last longer. Additionally, CBD blocks the breakdown of THC to its metabolite 11-OH-THC, thereby decreasing some of the psychoactivity and sedation associated with this metabolite. Due to the entourage effect, CBD's properties are enhanced when other cannabinoids and terpenoids are present.

In my clinical experience, patients who benefit the most from CBD-rich chemovars are those who want to minimize the psychoactivity of cannabis use and who have inflammatory illnesses, autoimmune disease, epilepsy, cancer, gastrointestinal disorders, anxiety and/or depression and psychosis. Because all CBD-rich cannabis plants (not hemp) contain some THC, knowing how much CBD and THC that are in the plant or product is important so that the CBD:THC ratio can be calculated. Knowing this ratio allows patients to determine potential psychoactivity.

Many patients use CBD-rich cannabis on a daily basis, one to three or more

times per day, to keep inflammation or seizures under control. Others who feel they do not need daily medication may use CBD-rich cannabis on an as-needed basis to help mitigate the symptoms of migraines, mood disorders, episodic anxiety or pain conditions.

One particular patient that has had great success with CBD-rich medicine is an 18-year-old with rheumatoid arthritis, Crohn's disease and a concurrent seizure disorder. She began using CBD-rich oil, taken by mouth every 8 hours, with the goal of treating her seizure disorder. She became seizure free within weeks of starting the oil and, within about three months, her blood tests for the inflammatory disorders showed significant improvement. She was able to stop taking all other medications, which included anticonvulsants and biologics (medications that are injected to stop inflammatory conditions), both of which were not effective for her.

Another patient who reports excellent results with CBD-rich cannabis is an older woman who had severe traumatic injuries, including significant head trauma, after a car accident. It took her two years to rehabilitate and she continued to suffer from chronic pain and intermittent depression that was not responding to conventional pharmaceuticals. She began using THC-rich medicine that eased her physical pain, but she did not find relief of her depressive symptoms. I encouraged her to add CBD-rich cannabis to her regimen and she found tremendous improvement in her mood. She only uses cannabis as needed and has been able to stay off of pharmaceuticals for over five years.

Important things to know about CBD:

- CBD-rich plants often contain over 4% CBD; the amount of THC will vary in these plants (most THC-rich chemovars have less than 2% CBD).
- When CBD potency is higher than THC potency, CBD acts to suppress some of the psychoactivity, rapid heartbeat and memory issues associated with THC.
- Plants that are higher in CBD potency and lower in THC potency are usually not psychoactive unless large doses are taken.
- CBD is often more effective when some THC is present due to the entourage effect.
- Industrial hemp-derived CBD lacks other cannabinoids and terpenoids, thereby losing the very important and beneficial entourage effect.

Names of some well-known CBD-rich cannabis varieties:

- AC/DC

- Cannatonic
- Harlequin
- Charlotte's Web
- Omrita
- Jamaican Lion
- Sour Tsunami
- CBD Crew
- Yummy
- CBD Medi-Haze

Remember that analytical testing of the cannabinoids is the only way to know the accurate content of any particular plant!

Other Important Phytocannabinoids

Effects of Cannabinol (CBN)

Cannabinol (CBN) is the third most prominent phytocannabinoid after THC and CBD. CBN is found in only trace amounts in the freshly cut cannabis flower. Unheated raw cannabis contains THCA (Delta-9-Tetrahydrocannabinolic acid) which, when heated up, converts to THC. CBN results from the oxidation of THC as it degrades.

CBN is weakly psychoactive. It has pain relieving and antibacterial properties. It also promotes bone growth and reduced eye pressure. CBN is thought to be sedating, however this effect is due to the loss of certain terpenoids which occurs when cannabis ages. The terpenoids that remain in the aging plant material are responsible for the sedating effect.

Effects of Delta- 9-Tetrahydrocannabinolic acid (THCA)

THCA is the main cannabinoid found in large amounts in raw unheated cannabis flower. When this compound is exposed to heat (about 230°-300°F) it is converted to THC by a process called decarboxylation. THCA is not psychoactive. Studies show that THCA is a potent anti-inflammatory. Other medicinal properties include antispasmodic, anti-tumor and anticonvulsant. Additionally, THCA blocks anticipatory nausea (a type of conditioned nausea that occurs when a person who has terrible nausea from chemotherapy develops nausea upon thinking about the future chemo treatment).

A number of my patients are using THCA successfully for inflammatory conditions and for seizure disorders. Some also find relief from pain, including nerve pain, which is notoriously difficult to treat. Some patients have reported excellent results from regularly drinking juices made from raw cannabis flowers and leaves. This method of taking THCA is challenging, as a large number of plants are required to regularly juice fresh leaves. Fortunately, THCA-rich sublingual cannabis tinctures and oils have become available over the past few years.

Effects of Cannabidiolic acid (CBDA)

CBDA is the precursor cannabinoid to CBD and is found in the unheated raw cannabis flower. Heating of CBDA converts it to CBD. CBDA is non-psychoactive. Only a few scientific studies have researched the medicinal effects of CBDA. CBDA combats nausea in multiple animal studies. CBDA has been shown to be a selective cyclooxygenase-2 (COX-2) inhibitor – this means it blocks the production of a compound we make in our bodies called prostaglandin. Prostaglandin is responsible for causing pain and swelling associated with inflammation. There is only one pharmaceutical COX-2 inhibitor available in the US (called celecoxib, brand name Celebrex) and it has side effects that include heart attack, stroke and intestinal ulcers. CBDA, taken by ingesting the juice made from a CBDA-rich cannabis plant or by a cold extracted oil, could potentially substitute for this pharmaceutical. CBDA has also been found in one laboratory study to act as an inhibitor of breast cancer cell migration, meaning it blocked the spread of aggressive breast cancer cells. This study showed that CBDA turns on a chemical compound that inhibits cancer cell mobility. A small number of suppliers have begun carrying cannabis oils rich in CBDA.

Effects of Tetrahydrocannabivarin (THCV)

THCV is another plant cannabinoid that has beneficial medicinal effects. At low

doses, THCV is a neutral antagonist of the Type 1 cannabinoid receptor, meaning it binds to the receptor, causing no effect on its own, while blocking other compounds from acting on the receptor. At higher doses it binds to and activates the Type 1 cannabinoid receptor. However, patients who have used chemovars that are high in THCV have reported its effects to include appetite suppression, anti-anxiety, anticonvulsant, tremor reduction and pain relief. THCV is reported to be psychoactive but in a recent study, participants who received THCV could not distinguish it from a placebo. In the same study, subjects reported that when given both THCV and THC together, the effects of THC were weaker or less intense. THCV is being investigated as an "anti-obesity" agent as it suppresses appetite and has been suggested as an excellent choice for those suffering with PTSD due to its ability to block panic attacks. It has also been recommended for treatment of tremors related to Parkinson's disease. Cannabis varieties reported to have higher amounts of THCV are currently quite rare and may include Malawi Gold, Doug's Varin, and Durban Poison.

Effects of Cannabidivarin (CBDV)

Cannabidivarin is a non-psychoactive cannabinoid that has been shown in numerous animal studies to work as an anticonvulsant by itself and additively when combined with CBD. It is well tolerated in an initial clinical trial for adult epilepsy in Europe and currently is in the early stages of research for its effectiveness and proper dosing for both adult and pediatric epilepsy.

How to Read and Understand Cannabis Testing Results

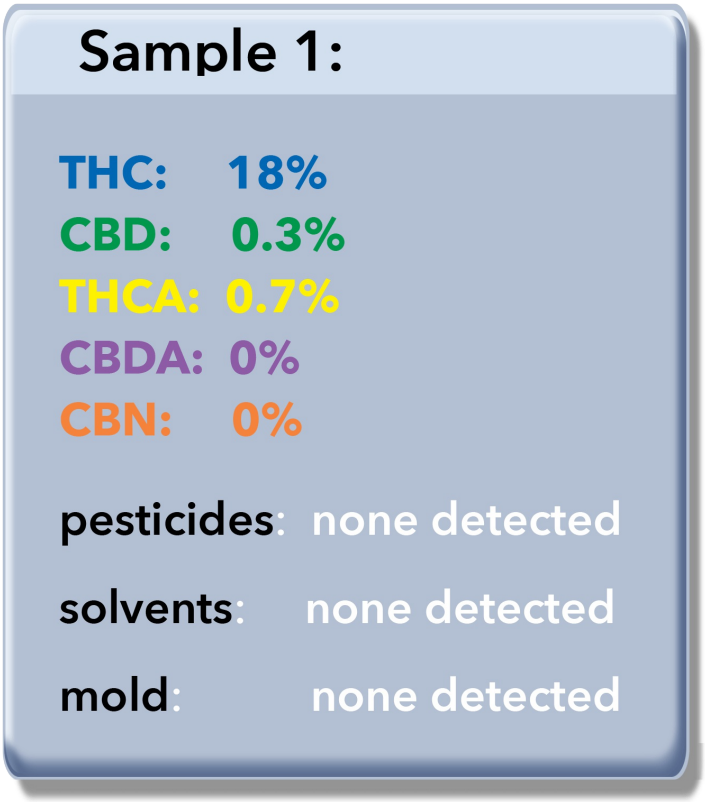
Cannabis chemovars and products can and should be tested so patients can be assured of the quality of their medicine. Cannabis testing includes the following information:

- Potency of cannabinoids ("cannabinoid potency")
- Profile and potency of terpenoids ("terpenoid potency")
- Presence of residual solvents
- Presence of bacteria and mold
- Presence of pesticides

Sample test result of THC-rich product:

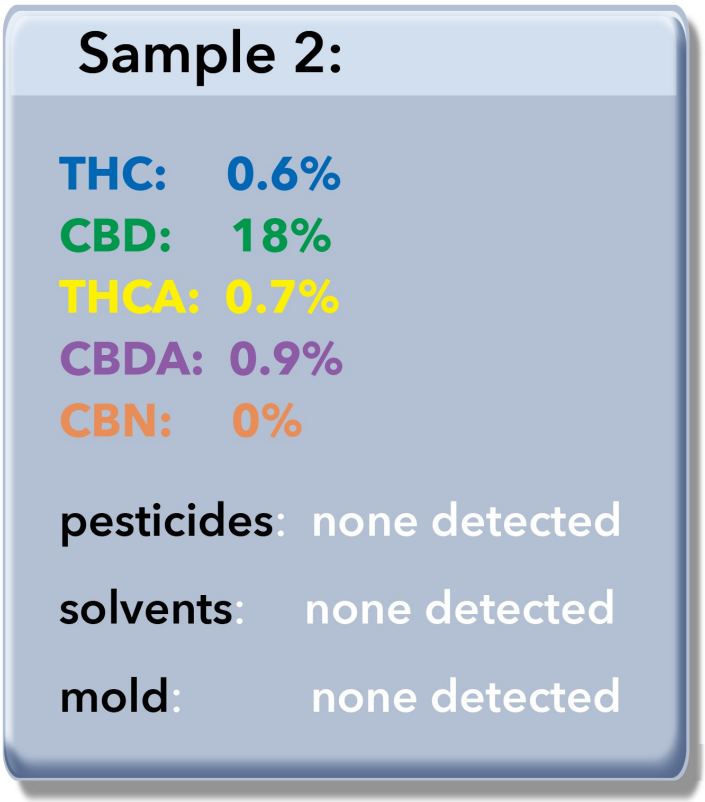
Sample 1 shows test results for a product that is THC rich (18%) and almost devoid of CBD (0.3%). The CBN content is 0%, which reflects that this test was performed

shortly after the flower was harvested. With very little CBD, this product will have dominant THC effects and significant psychoactivity for most (depending on the user's tolerance to THC). Medicinal effects include pain relief, reduced anxiety and depression, relief from nausea and vomiting, enhanced appetite, and lowered intraocular pressure. Importantly there were no pesticides, solvents or mold detected in this sample.



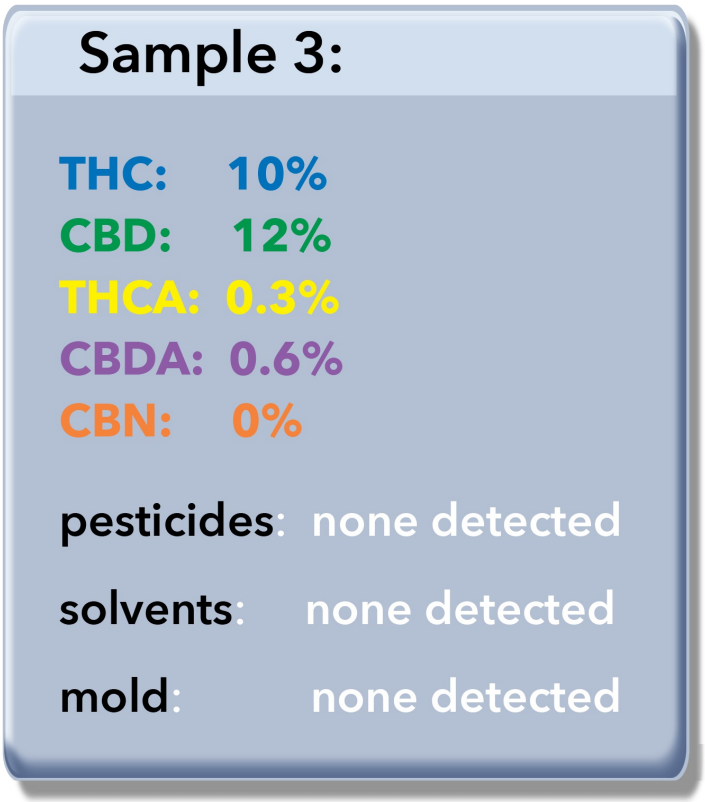
Sample test result of CBD-rich product:

Sample 2 shows test results for a product that is quite different than Sample 1. Since the CBD content is quite high at 18% and the THC content is very low (0.6%), this chemovar will have dominant CBD effects, such as pain relief, lessened anxiety and depression, anti-convulsant and anti-inflammatory effects without psychoactivity. You can determine the CBD:THC ratio by dividing the percent of CBD by the percent THC: 18% divided by 0.6% results in a ratio of 30 parts CBD to 1 part THC (more on this later in the chapter). Again it is important to note that no pesticides, solvents or mold were found when the product was tested.



Sample test result of mixed product:

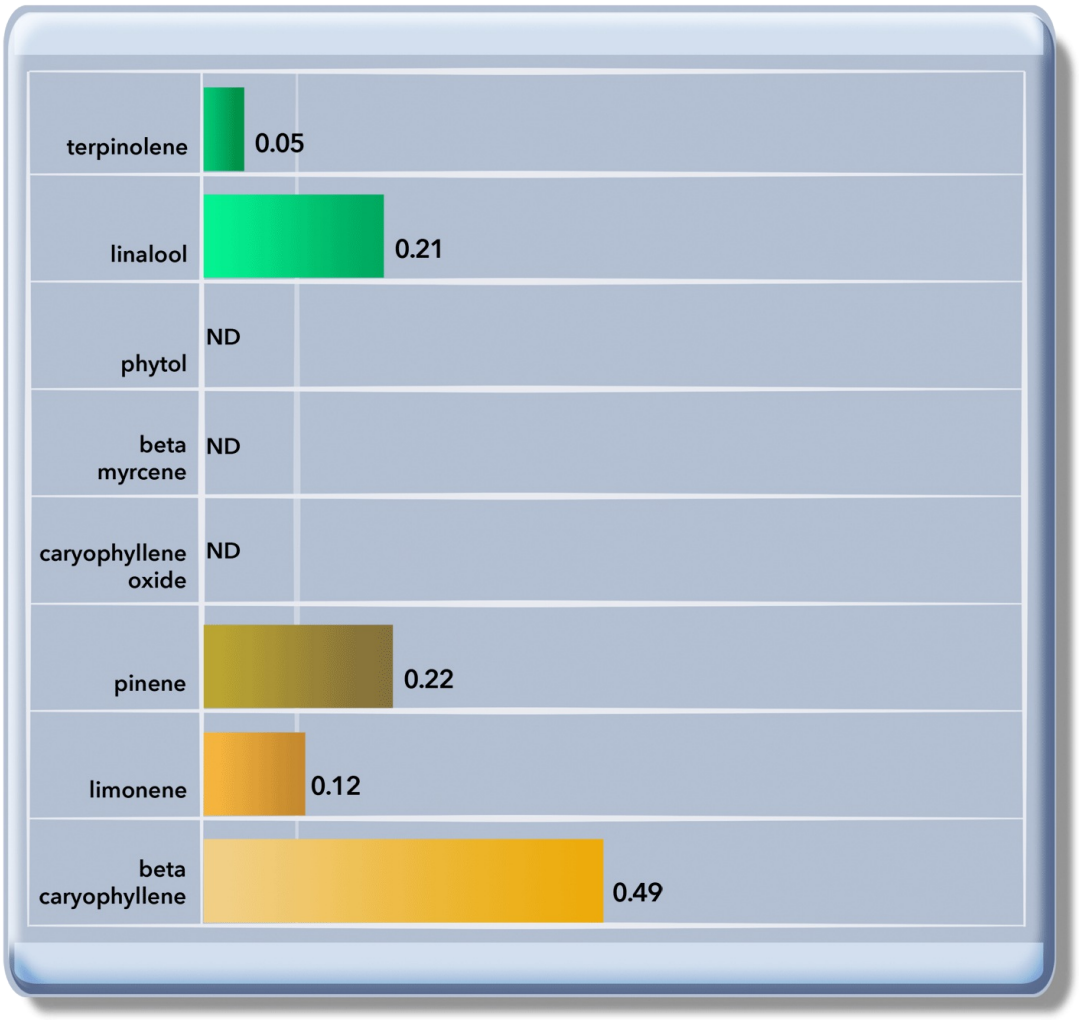
Sample 3 shows test results for a product that has almost equal amounts of CBD and THC. The CBD will mitigate some of the THC effects and result in less psychoactivity; however, some of the effects of this chemovar will depend on the user's previous experience with cannabis. A person who uses cannabis on a regular basis would likely have less psychoactivity than someone who is inexperienced or new to cannabis use. This chemovar has the medicinal effects of pain relief, relief from nausea and vomiting, lessened anxiety and depression, anti-inflammatory and may be anti-convulsant for some.



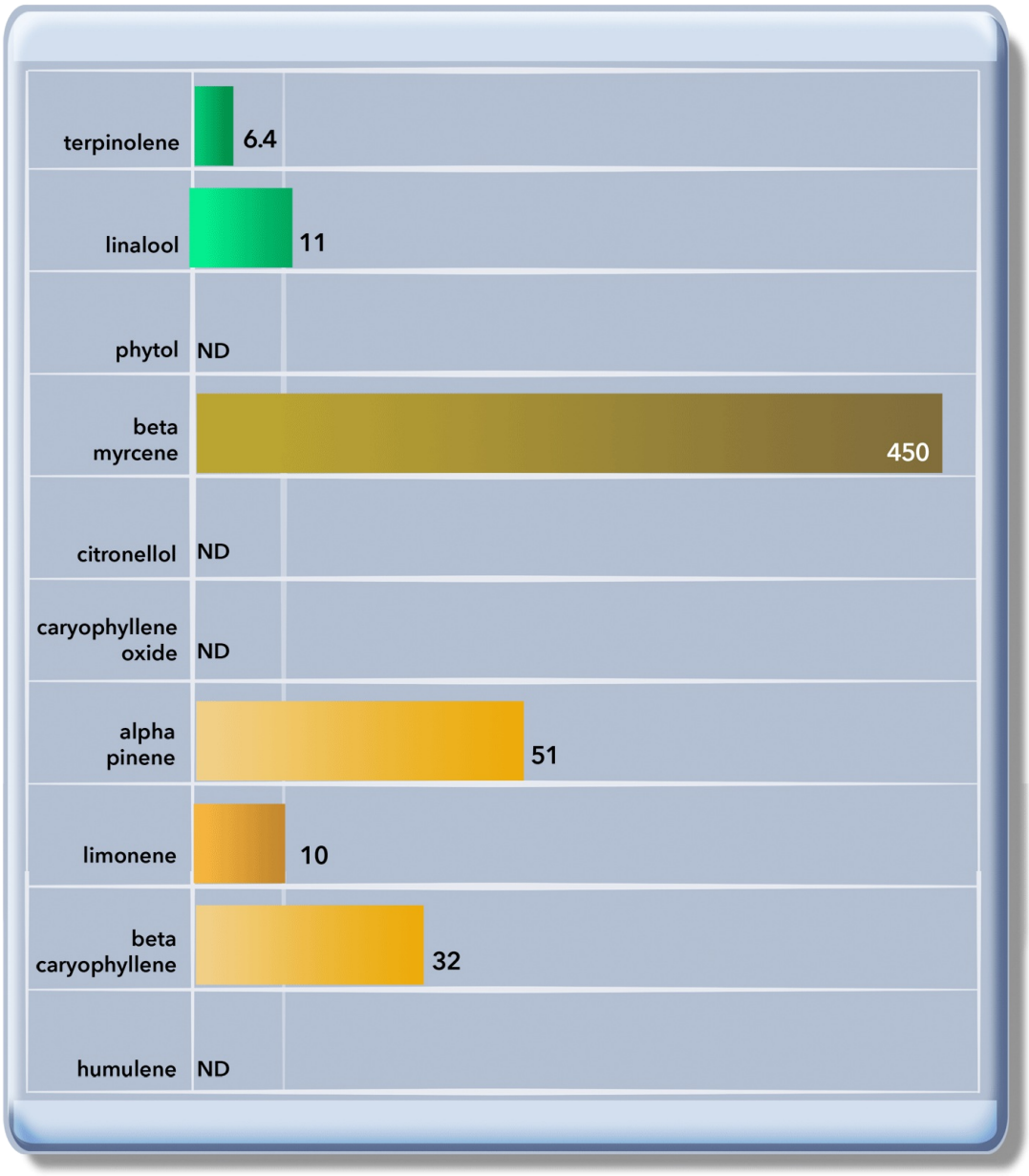
As you can see, the cannabis plant is very diverse in its expression of CBD and THC. Most patients have to try a number of different products that contain different CBD and THC amounts to find what works best for their particular medical condition.

Terpenoid Profiles

Here are examples of terpenoid tests on two different cannabis chemovars:



Chemovar 1: Terpenoid Profile in milligrams per milliliter (mg/ml)



Chemovar 2: Terpenoid Profile in milligrams per milliliter (mg/ml)

If you compare the two test results, you can see they have different terpenoid profiles. Chemovar 1 contains β-caryophyllene (anti-inflammatory, pain relief, intestinal relief), pinene (anti-inflammatory, focus and memory enhancer) and linalool (anti-anxiety, pain relief) as its three most common terpenoids. The β-myrcene content is not detected (ND) and therefore this chemovar is likely to not be sedating.

Chemovar 2 contains a large amount of β-myrcene (sedating, analgesic) with some pinene and β-caryophyllene, both of which are anti-inflammatory. This chemovar is likely to be sedating with some pain relieving properties.

Testing for Residual Solvents

Solvents are often employed in the manufacturing of cannabis extracts and concentrated preparations. Solvents that are not purged properly and leftover in the end product are called "residual solvents." Butane, propane, pentane, hexane, and naphtha, all of which are petroleum derivatives, highly flammable and potentially carcinogenic, are being used by some suppliers to make concentrates and extracts.

Although some cannabis experts claim that professional butane extraction is safe and results in a clean product, the majority of butane-processed extracts are being made by laypersons, not chemists, who are not operating within a laboratory setting. The result can be a product that contains residual solvent.

Additionally, the final products made with these compounds often have lower levels of terpenoids, which can decrease the medicinal benefits for some patients. I do not recommend products made with these chemicals, unless testing by a reputable lab reveals no residual solvent.

Ethanol is also used as a solvent for concentrates and extracts. Ethanol is safe for consumption by adults and the final products often have high terpene content. However, a process called supercritical carbon dioxide (CO_2) extraction is becoming quite popular as no harmful solvents are used and the end product is solvent-less. CO_2 extraction is considered by many to be the cleanest and most safe extraction method. CO_2 extraction may result in excellent terpenoid content when compared to butane extraction although many believe the latter to be superior. No matter what process is used, all concentrates and extracts should be tested for residual solvents so patients can be assured of the purity of the product.

Residual solvent amounts are often expressed in parts per million (ppm). For example, the state of Colorado requires testing of all concentrates and extracts with butane and propane residual solvent levels to be less than 50 ppm, and heptane, isopropranol and ethanol levels to be less than 10 ppm.

A few years ago, a mother brought her son to see me for severe symptoms related to autism. She brought a syringe containing concentrated cannabis oil that her neighbor had made and given to her. She had not used the oil, as she was nervous about using cannabis without talking to a physician first. I insisted that the product be tested for potency, residual solvent, pesticides, mold and bacteria before use. The oil was found to contain 94,000 parts per million isopropanol. **This is over 9,000 times the permissible level allowed in Colorado!**

Isopropanol and its metabolite acetone have been shown to cause central nervous system depression, nausea, vomiting, dizziness, respiratory depression and coma. This is an all too common example of non-chemists manufacturing cannabis products with the potential to make people sick. It is imperative that patients only use tested cannabis products!

Testing for Microbes (fungi and bacteria)

Cannabis can be contaminated with bacteria or fungi (yeast or mold) at any point in the growing or product manufacturing process. Contaminated cannabis can be dangerous, especially for those with compromised immune function. Bacteria and mold can be identified by using plating, whereby prepared samples are placed on growth medium and incubated; any growth is counted and reported as "Colony Forming Units Per Gram (CFU/g)." Another process called quantitative polymerase chain reaction (qPCR) utilizes machinery that extracts DNA from the microbes, which is then genetically sequenced to identify the organism. States that mandate cannabis testing vary in permissible levels of microbial contaminants. For example, Colorado requires products to test negative (meaning no detection) for most molds and bacteria but Washington testing mandates that "Total Combined Yeast & Mold Count to be not more than 1,000 CFU/g."

Testing for Pesticides

The cannabis plant is like any other plant, prone to disease and infestation by pests. Chemicals such as insecticides, herbicides, and fungicides are being used by many growers despite the fact that most patients do not want these chemicals in their medicine. There has been no research investigating the side effects from pesticides inhaled or ingested specifically related to cannabis use. However, studies clearly show that pesticides have been linked to cancer, skin irritation, endocrine dysfunction, neurologic disorders including Alzheimer's disease and ADHD, reproductive problems and birth defects.

States where cannabis is legal for medical and/or recreational use have allowed for certain pesticides based on previous approval for use on food intended for human consumption. I strongly recommend that you avoid these chemicals in your food and in your cannabis!

Although cannabis analytic laboratories can test for many different types of pesticides, it is not mandated in most cannabis states. In a recent investigation, 26 cannabis samples were purchased from legal stores in the state of Washington. Pesticide analysis at a state certified legal licensed laboratory revealed that 22 tested positive for pesticides!

There is a burgeoning interest in organic cannabis farming. However, the USDA still does not recognize cannabis as a legal crop and organic certification agencies are prohibited from certifying cannabis from these growers. Until such certification exists and pesticide testing is mandated, patients should seek out and only obtain cannabis that has been tested for pesticides by a responsible supplier or collective.

Different Delivery Methods for Cannabis Medicine

Many potential cannabis patients are turned off by the idea of smoking. You do not have to smoke cannabis to get the benefits! There are many different ways to use cannabis as a medicine, but it is important to understand how the different delivery methods may change the effects.

Inhalation

With inhalation, the maximum blood concentration of THC occurs within minutes. The psychoactive effects start within seconds to a few minutes, reach a peak effect in 30 minutes and taper off within 1-4 hours, depending on the dose.

The advantages of inhalation include rapid onset of effects and easier dosing. Since effects are felt fairly quickly, most patients are able to adjust their dose to the desired effect and therefore unwanted side effects are minimized.

Vaporization is much preferred over smoking as it eliminates the toxins from the burning plant matter and reduces the resultant irritation to the lungs. Despite the belief that bongs or water pipes act as a "filter," they actually do not decrease the amount of tar or other particles in the smoke. In fact, water pipe or bong smokers actually inhale 30% more smoke to get the same effect as a pipe or joint. Although THC is not water soluble, the water traps THC without trapping very much tar, so the "hit" that is inhaled has less medicinal compounds and more toxins. I do not encourage my patients to use bongs or water pipes.

Vaporizers

Vaporizers are devices that heat up cannabis and emit a vapor that contains the medicinal compounds without the products of combustion like tar, carbon monoxide and particulate matter. Widely considered to be a "cleaner" way to inhale cannabis medicine, vaporizing produces no smoke and virtually no toxins.

Advantages of vaporization of cannabis flower are:

- Smokeless way to inhale.
- More efficient use of medication.
- Quicker onset and easier to dose than non-inhalation methods.
- Less odor.
- Less toxicity for lungs and airway.
- Less risk of bronchitis and other respiratory symptoms (such as cough, wheeze, tightness in the chest).

Vaporizers work by heating the cannabis flower without burning it. THC, CBD and other cannabinoids and terpenoids will boil off and become a vapor between 315-360° F. This vapor is then inhaled without the contaminants contained in combustion. Vaporizers can create vapor by two different methods. With conduction, one places the cannabis flower on a surface that heats up like a hot plate, and the molecules of medicine in the flower that touch the hot surface will vaporize. With convection, air is heated up and then passed through the plant material, vaporizing the medicine. The cannabis flower should be ground up in both methods to improve the extraction of the medicine.

Some vaporizers heat ground-up cannabis flower, and some heat processed cannabis oil. Over the past few years, some patients and recreational users have started to use "e-cigarette" type vaporizers, also known as pen vaporizers. In order to use these devices, the cannabis flower must be processed into a liquid form, usually an oil, that is then placed into a cartridge or chamber and inserted into the e-cigarette device.

Residual solvents may be left in the final product during the manufacturing of oils for use in these vaporizers. Other additives such as propylene glycol and glycerine may be present and with heat, will change to formaldehyde. As mentioned earlier, I recommend that you avoid products that may contain residual solvents or these additives. Oils that are processed using the supercritical CO2 method are generally considered to be safe. If there is any doubt about a product that you want to use, inquire about testing results or have a sample tested by a laboratory to ensure that it is clean and safe.

In terms of dosing, it is difficult to know the exact milligram dose when inhaling cannabis by smoking or vaporizing. However, with practice, most patients that inhale find they can easily medicate without fear of overdosing. One should and must use caution if the product is considered a concentrate as the potency can be quite high, causing an overdose for an inexperienced patient.

Oral Ingestion

When cannabis is ingested through drinks or edibles, the onset of effects begin after 30-90 minutes, but they can vary widely person to person. The effects reach their peak in 2-3 hours and last for approximately 6-8 hours, depending on dose.

THC absorbed through the intestinal tract will pass through the liver. This is called the "first pass effect." Much of the THC will be broken down to a cousin compound of THC, called 11-hydroxy-THC, which is psychoactive on its own and, when combined with THC, increases the potency of the psychoactive effects. Ingestion produces a different effect than inhalation for most cannabis

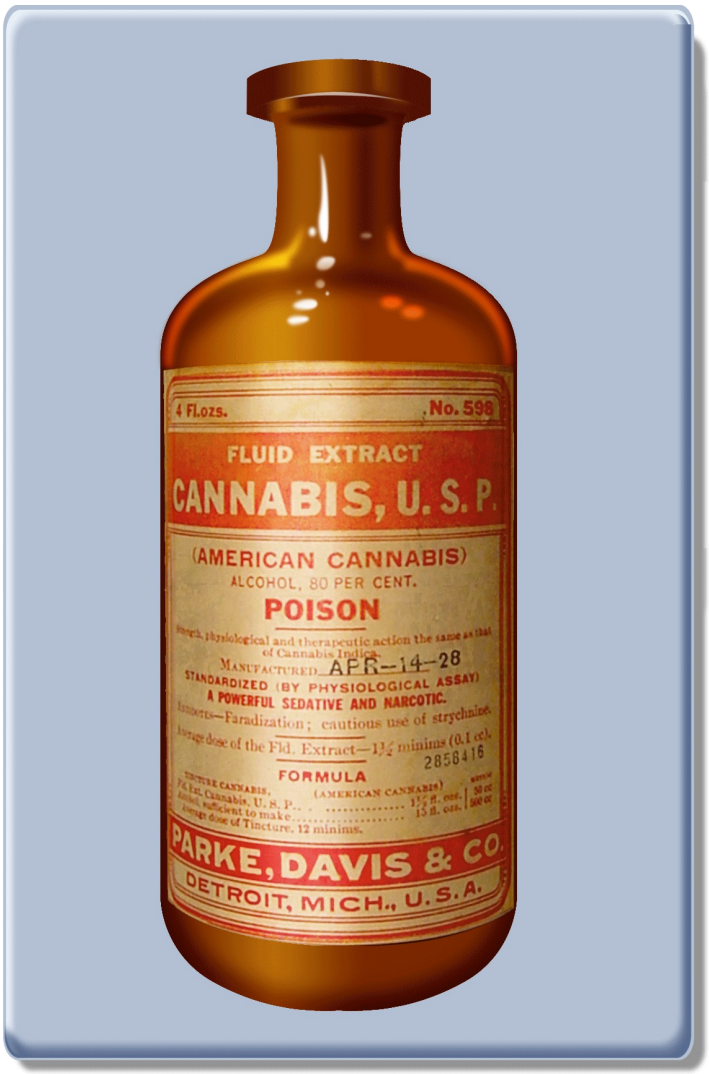
users, with the effects described as "more relaxing" or as a "body high." Some patients prefer this effect and others do not.

The advantages of ingestion are that smoke is avoided, there is no need for equipment such as a vaporizer, the duration of effect is longer and there is no odor. Edible forms of cannabis can be taken discreetly. **Due to the variation in bioavailability (how much you absorb) and in the products themselves, dosing of edibles is more difficult.**

Medical cannabis patients are advised to start with **very small amounts** (especially for THC-rich edibles), wait for at least 90 minutes and repeat the dose if no effect is felt. Since ingested THC is metabolized to the more potent 11-hydroxy-THC in the liver, new or inexperienced users can easily overdo it. The effect from edibles can be quite potent, even with small amounts. **In fact, the most common reason for cannabis overdose symptoms (increased heart rate, anxiety, excessive sleepiness, hallucinations or paranoia) is the ingestion of too much of an edible THC-rich cannabis product.** That being said, many patients do very well with edibles when they have been educated on the proper way to dose them.

In most states where medical cannabis is legally available, edible products are tested and labeled with potency of THC, CBD, CBN, THCA, CBDA and occasionally with the terpenoid profile. Always check the wrapper for the potency information, as it can be quite helpful in figuring out the dose. I recommend using ONLY cannabis products that are properly tested and labeled.

Sublingual Tinctures



Cannabis Tincture, 1928

Cannabis tinctures or extracts have been made for hundreds of years. Pharmaceutical bottles of cannabis tincture that were made in the 1920s report on the label that cannabis is an "analgesic" and a "powerful sedative."

By definition, tinctures are alcohol-based liquid concentrates, and extracts are oil-based liquid concentrates. In the cannabis industry, however, the terms tincture and oil are often used interchangeably. Most patients use these products sublingually (under the tongue) where they are quickly absorbed through the mucus membrane in the mouth. The medication goes directly to the bloodstream, bypassing the liver and avoiding the first pass effect described above. Effects are usually felt within 15-60 minutes and can be similar to those from inhaled THC. The liquid can be dispensed with an eyedropper, a needle-less syringe, or a sprayer. Most patients start with a small number of drops or sprays and increase the dose until the desired effects are achieved.

Another sublingual form of cannabis is the dissolvable strip, similar to breath strips. Patients often start with a small piece of the strip, which is then

placed under the tongue. The dose may be repeated, with a wait time of at least 60 minutes before taking more if no effect is felt. The effects can be similar to inhaled cannabis.

Advantages of sublingual forms of cannabis are the avoidance of smoke, faster absorption than orally ingested forms, a minimal first pass effect in the liver, no odor and discreet use. In addition, patients can make their own tinctures and extracts out of their preferred chemovars if they choose to do so. Another very important advantage is that patients who require higher doses of THC or CBD can use concentrated cannabis oils to deliver larger doses in small volumes.

I recommend only using tinctures that are tested and properly labeled. Reading the label will tell you how many milligrams of THC and CBD are in one spray or one milliliter (ml).

Pediatric patients and patients with disabilities may not be able to cooperate with certain delivery methods. I have found that tinctures work well for these patients as they can be taken by mouth, hidden in food, or even given through a gastrostomy tube. Concentrated tinctures are also advised as a larger milligram dose in a smaller volume is easier for patient compliance.

Dermal/Topical

Cannabis can be made into ointments, salves, lotions and alcohol preparations and applied to the skin to treat local pain (such as in arthritis) or rashes (such as psoriasis or eczema). These preparations have been used in India and Latin America for hundreds of years with reports of significant pain relief, especially for joint pain and for relief of certain skin rashes. There is evidence that topical cannabis is effective treatment for skin infections such as MRSA, a resistant type of bacterial skin infection.

Psychoactivity with topical cannabis use is rare. Preparations are currently available that are THC-rich, CBD-rich or a combination of both cannabinoids.

A number of scientific studies researching the effects of topical preparations of cannabis demonstrated the following:

- Topical applications of THC helped mice heal faster from skin allergies.
- Topical extracts were shown to have anti-inflammatory properties in laboratory animal experiments.
- Five major phytocannabinoids showed potent activity against MRSA.
- Synthetic topical cannabinoids relieved pain experienced by patients suffering with post-herpetic neuralgia.
- Topical application of THC was found to decrease allergic inflammation in a model of contact dermatitis (eczema).

- A recent study using CBD gels in various doses applied to rats with arthritic knee joints found significant reduction of joint swelling, immune cell infiltration and less thickening of the synovial membrane.

Many of my patients use topical preparations successfully for arthritis, especially on the smaller joints, such as hands, feet, elbows, and knees. Some patients report relief of bursitis pain, plantar fasciitis pain and scar tissue pain. A few patients even find relief of neck and low back pain and a few report that nerve pain responds as well. Contact dermatitis, psoriasis and eczema have all been successfully treated with topical cannabis (alcohol based products should be avoided in these cases). There are anecdotal cases of patients applying cannabis to precancerous or small cancerous lesions with resolution of the lesions.

Topical preparations are not standardized and vary widely in ingredients, chemovars used, and potency. Sometimes patients have to experiment with a few different preparations to find the one that works best for their condition.

Since there have been a few cases of allergic reactions to topical cannabis products, I recommend applying a small amount as a test before applying to a larger area of skin.

Rectal Suppositories

Although there are many people that report good results using cannabis suppositories, there is no scientific evidence that absorption of THC occurs through rectal delivery. A study of rectal cannabis suppositories used in monkeys reports that THC is not absorbed rectally. However, when a chemical compound called hemi-succinate is combined with THC, absorption is double that of oral ingestion of THC. These types of suppositories were used in the lab only and are not available to patients yet. I rarely recommend THC-rich cannabis through the rectal route because we are still uncertain of the amount of medicine that gets into the system. Very little research about CBD via the rectal route exists, but one study found that rectal CBD reduced colitis (inflammation of the colon) in mice.

Transdermal Patches

Transdermal patches of cannabis are of great interest to patients as this method of delivery has many benefits, especially when compared to oral delivery of cannabinoids. Compliance is easier for most patients and first pass effect through the liver can be avoided. One problematic issue with patches is that cannabinoids are fat-based compounds that do not mix with water and the aqueous layer of the skin may interfere with absorption into the bloodstream. If permeation enhancers, which are compounds that promote the flow of the drug through the skin, bioavailability is improved. A few studies have looked at

the use of permeation enhancers with cannabinoids and I expect that in the near future, a number of cannabinoid patches with different cannabinoid profiles will be available for use.

Ratio And Concentration

Figuring out which cannabis preparation to take can be confusing. When searching for cannabis medicine, two terms – ratio and concentration – are important to understand.

Ratio

Ratio tells how much CBD is in relation to THC in a particular cannabis plant or preparation.

If a cannabis plant or product lists a ratio or the word "CBD" on its label, it contains some amount of CBD. If there is no ratio or the word "CBD" is not listed on the label, it is very likely a product high in THC and has negligible amounts of CBD.

If a cannabis product is labeled 5:1 CBD:THC, it contains 5 parts CBD to 1 part THC. Said another way, it has 5 times more CBD than THC. If the product is labeled 20:1, it contains 20 parts CBD to 1 part THC and has 20 times more CBD than THC.

Knowing the ratio allows patients to determine whether the product will cause psychoactivity and what the effects are likely to be. In general, for inexperienced users, ratios over 10:1 CBD:THC (for example, 10:1, 15:1, 20:1, etc.) will not cause psychoactivity. Ratios under 10:1 can cause psychoactivity for some patients.

The ratio of CBD to THC is most important for those patients who do *not* want to experience psychoactivity, or for those who want the benefits of both of these amazing compounds.

Concentration

Concentration tells how much CBD and THC in milligrams (sometimes expressed as percent) are in the plant or preparation. Knowing the milligrams of CBD and THC leads to calculating the ratio.

For example, if you have a bottle of cannabis oil that has 20mg of CBD per 1 milliliter (mL) of oil and it also has 10mg of THC per 1mL of oil, the ratio can be calculated by dividing 20mg of CBD by 10mg of THC, which equals 2:1. This oil has 2 times more CBD than THC.

Knowing the concentration not only helps the patient figure out the ratio, but also helps with proper dosing. In the example above, the oil has 20mg of CBD per 1mL. If your healthcare professional recommended that you take

10mg of CBD, you would take 0.5mL of the oil to get this dose.

Be aware that just knowing the ratio *does not* tell you the milligrams in the product. A 2:1 CBD:THC product may have 20mg of CBD and 10mg of THC, but it could also have any amount of CBD that is two times more than THC (for example 100mg CBD and 50mg THC will also have the same 2:1 ratio). However, if you know the milligram concentration of both CBD and THC, you can always determine the ratio by simple division.

In sum, knowing the ratio allows you to know the likely effects of the product and knowing the concentration allows you to correctly dose in milligrams.

Cannabis Dosing: Start Low And Go Slow

There is a wide therapeutic range for cannabinoid dosing. Patients respond to certain chemovars or preparations in a unique way, and there are too many variables, such as your metabolism, the delivery method, dose, cannabinoid ratio and product formulation, for dosing of cannabis to be standardized.

Dosing of cannabis is not "one size fits all". It is highly individualized and has been called "patient-determined, self-titrating" by many experts.

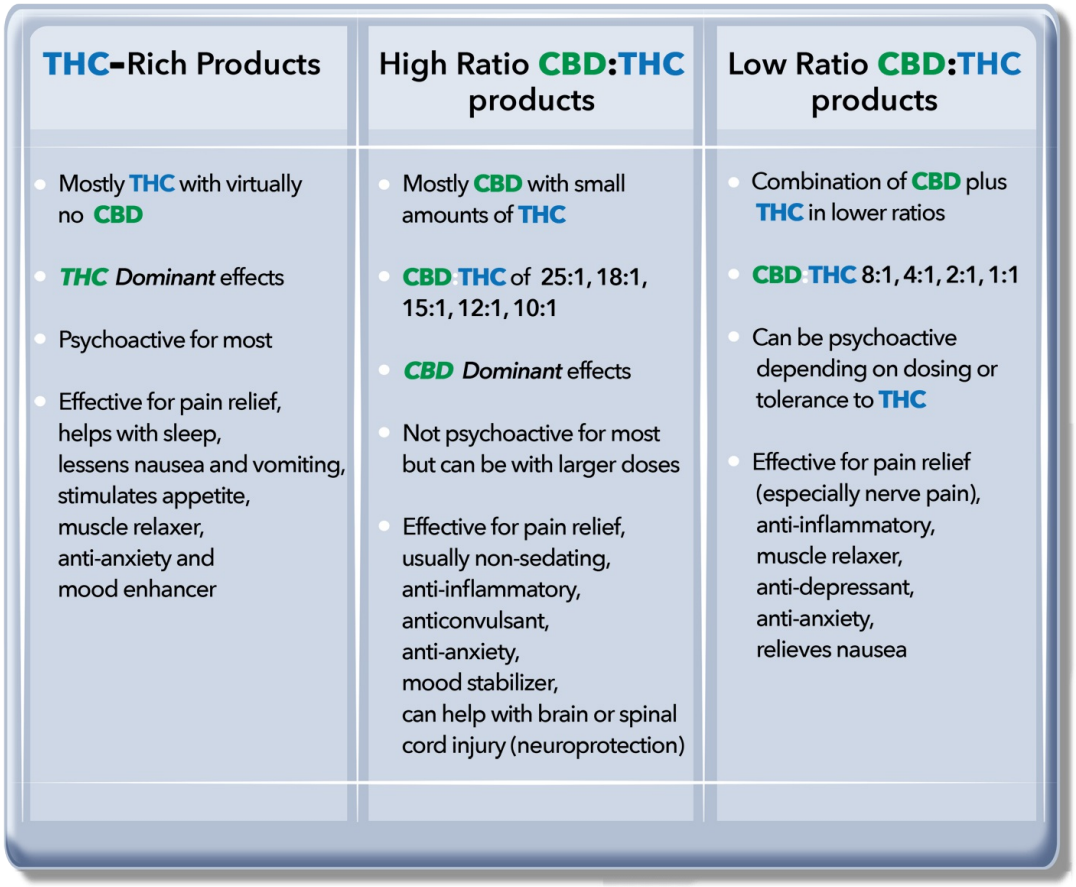
The general rule of thumb is to start with a low dose and increase slowly so you can find the dose that helps your medical condition without going overboard. This takes trial and error and usually requires trying different products, ratios and doses to find what works. If you are new to cannabis use, you should wait at least 30-90 minutes before re-dosing, depending on the method of delivery, as you must give the medication a chance to get into your system. Inhalation will give fairly immediate results but all other methods require time for the effects to be felt.

Patients have complained to me in recent years that there are too many cannabis products to pick from and they are overwhelmed when trying to choose their medicine. I teach them a simple approach that is methodical and allows them to find what works and what doesn't.

- Decide what delivery method you want to try first. Be aware that you may need to try a different delivery method depending on your response but start with a method that is most comfortable for you.
- Think about what effects you are looking for – are you looking for sleep or pain relief or seizure control? Knowing this will help you decide on whether to start with a THC dominant product versus one containing CBD (with either CBD dominant effects or combination effects). Using the chart below, you can look at any product and categorize it by its test results. Knowing which category the product falls into will let you know the likely effects.
- Take a small dose and wait for the effects. Re-dose only if the effects are not felt. It is better to take multiple small doses throughout the day rather than one large dose.
- Give yourself a few days at a certain dose before changing doses or products.
- Keep a log of what you are taking, the dose amount and the dose timing so that you can assess which products worked, what doses worked and

how long the effects lasted.

The following chart helps my patients figure out the likely effects of cannabis products:



THC-Rich Products	High Ratio CBD:THC products	Low Ratio CBD:THC products
• Mostly THC with virtually no CBD • *THC Dominant* effects • Psychoactive for most • Effective for pain relief, helps with sleep, lessens nausea and vomiting, stimulates appetite, muscle relaxer, anti-anxiety and mood enhancer	• Mostly CBD with small amounts of THC • CBD:THC of 25:1, 18:1, 15:1, 12:1, 10:1 • *CBD Dominant* effects • Not psychoactive for most but can be with larger doses • Effective for pain relief, usually non-sedating, anti-inflammatory, anticonvulsant, anti-anxiety, mood stabilizer, can help with brain or spinal cord injury (neuroprotection)	• Combination of CBD plus THC in lower ratios • CBD:THC 8:1, 4:1, 2:1, 1:1 • Can be psychoactive depending on dosing or tolerance to THC • Effective for pain relief (especially nerve pain), anti-inflammatory, muscle relaxer, anti-depressant, anti-anxiety, relieves nausea

As you can see, there is overlap in the medicinal effects of the three categories. Many patients who have experience with THC in the past are less fearful of the effects of THC and therefore may choose products with more THC, whereas someone new to cannabis use may be nervous about THC effects and will be more likely to start with high ratio CBD:THC products. There is no wrong choice. You should go with what feels right for your situation and then depending on your response, you can switch products to fine-tune the results. As mentioned above, start low and go slow. Once you have a product, you can use the following dosing guidelines to help figure out a starting dose.

When I meet with my patients, I often show them examples of product wrappers in order to teach them how to figure out which of the above categories the product falls into, and that way they can know the likely effects. This also allows patients to avoid a possible THC overdose, which although it is never fatal, it can be uncomfortable.

Here is a wrapper from a medical cannabis product:

THC potency is 25mg per 1mL and CBD potency is 1mg per 1mL. This is a

THC-rich product, which can cause significant psychoactivity if not dosed correctly. For most new or inexperienced users of edible cannabis products, a starting dose of no more than 2.5mg THC is recommended. For this product, only 0.1mL (one tenth of a mL) is equal to 2.5mg.

Here is another wrapper from a medical cannabis product:

THC potency is 2mg and CBD potency is 50mg. This is a CBD-rich product with a ratio of CBD:THC of 25:1 (take the CBD potency and divide by the THC potency). A product such as this is unlikely to cause any significant psychoactivity as the total THC of 2mg is lower than the recommended starting dose of 2.5mg. A starting dose of 10mg CBD is recommended. For this product, one-fifth of the product is equal to 10mg.

Here is a wrapper from another medical cannabis product:

THC potency is 15mg and CBD potency is 15mg. This is product with a ratio of CBD:THC of 1:1 (take the CBD potency and divide by the THC potency). A product such as this is may cause psychoactivity in a new or inexperienced patient. This product should be divided into 6 separate pieces in order to get 2.5mg THC and 2.5mg CBD. Since the THC effects of this

product may be strong for some patients, the recommended approach is to start at a low dose and and wait for the effects, only taking another small dose if no effects are felt.

The following doses are guidelines only and may vary based on the medical condition being treated. Medical supervision is highly recommended prior to starting cannabis treatment. These doses are for adults only. Pediatric patients should not be using cannabis products without medical supervision.

THC dosing guidelines:

- 1mg up to 5mg per dose for new or inexperienced patients – it is recommended that you start with 1-2.5mg only, wait for the effects, and re-dose small amount only if desired effects are not felt. Most patients increase in increments of 2.5 mg until they reach the effective dose.
- 15mg+ for experienced patients depending on desired effect and tolerance.

CBD dosing guidelines:

- Wide range of dosing depending on medical condition.
- Low dose is about 10mg but can go as high as 200mg per dose for potent anti-inflammatory effects.

If you have a product with equal amounts of CBD and THC, use the THC dosing guidelines so as to avoid unwanted side effects from taking too much THC.

Be aware that patients with the same medical conditions can and will find different results even if using the same cannabis chemovar, same dose and same CBD:THC ratios. Using trial and error to find what works for your specific situation is the best way to obtain the best results. Using tested cannabis products is the only way to keep track of what works and what doesn't.

In my clinical practice, I have seen patients with the same medical conditions use different delivery methods and different doses. Why is that? Remember that each person has a unique metabolism and a unique endocannabinoid system resulting in a unique response to cannabis medicine. An example of this is a mother and adult daughter, both with long-standing debilitating migraine headaches, who came to see me. The daughter had experimented with cannabis prior to her office visit and she reported that if she vaporized THC-rich cannabis at the onset of the symptoms, the migraine did not progress and within 30 minutes all symptoms had disappeared. She shared this information with her

mother and encouraged her mother to try using the vaporizer in the same manner. Her mother found that the migraine headache pain increased with vaporized THC but sublingual application of a combination CBD+THC tincture eliminated her migraine symptoms. This example illustrates that even people who are genetically related can respond differently to different delivery methods and different combinations of cannabinoids.

First Time Use of THC-Rich Cannabis

Sometimes patients who have never used cannabis before may not feel any effect with first time use. These patients may get frustrated and take more, which can result in an undesirable "overdose" effect (tachycardia, excessive sleepiness, anxiety and/or paranoia). If you try cannabis medicine and don't feel anything, you can take another small dose but if you still don't feel anything, stop and try again another day. No one knows why some people don't feel the effects the first time, but we think the body may need to be exposed to the medication before the effects can be felt. Sometimes with first time use, too, a patient may deny feeling any effects, but those around the patient will notice the patient is acting differently.

The adult son of one of my breast cancer patients, who was suffering terrible side effects from chemotherapy, reported at a follow-up visit that the first time his mother used cannabis, she got out of bed (where she had been spending most of her time) and began to make dinner. She was chatty and happy for the first time in months and he said the whole family felt relief that "mom was back to normal." The fascinating part of this story is that when I asked the patient how cannabis made her feel, she said she didn't really feel anything unusual or different, she just felt like she could get up and make dinner. It was only after a few times of use over the course of a week that she was able to notice that she felt happier, had more energy and was back to a more regular routine.

Cannabis Overdose

Overdose is more common by the oral ingestion route as dosing by this delivery method can be difficult to determine and the breakdown product of THC is quite psychoactive and long-lasting. **There is no danger of respiratory arrest or death.** Overdose of THC can cause rapid heart rate, orthostatic hypotension, altered time perception, paranoia, anxiety, impaired motor coordination, delusional thinking, excessive sleepiness and/or a sense of impending death (perceived harm).

If you take too much THC-rich cannabis and feel badly from it, reassure

yourself that you are safe and that nothing bad is going to happen. Try to lie down and sleep or distract yourself with television. In Ethan Russo's terrific paper "Taming THC", antidotes for THC overdose are described and include cold lemonade, calamus root, pine nuts, and peppercorn, as all of these contain terpenoids that counteract the undesirable effects of the overdose. Also, CBD-rich cannabis can lessen the THC-induced overdose symptoms. Some patients seek care in the ER and can be treated with benzodiazepines for the anxiety. Once the cannabis wears off, there can be residual effects of lethargy and/or headache but these will usually resolve quickly.

Overdose can result in a patient's reluctance to use cannabis again but can easily be avoided by only using a small amount of THC-rich cannabis at a time and also using cannabis that contains CBD, which can buffer the psychoactivity of THC.

Medicinal Versus Recreational Use

I often explain to my patients that there are two ways to approach cannabis use. One is the recreational approach and one is the medicinal approach. The goal of recreational use is to "get high." The goal of a medicinal dose is to treat the medical condition. For some patients there is overlap, and the sensation of "feeling high" is truly a feeling of relief from physical and/or psychological pain. This is extremely valuable for many patients that are suffering, giving them much needed respite and an improvement in their quality of life.

For others, a smaller dose alleviates symptoms and psychoactivity can be avoided. Using a CBD-rich medicine (higher CBD:THC ratio) will prevent psychoactivity, but if relief is not achieved, adding THC may be helpful and should not be feared. A medicinal dose of THC can usually be found. Many of my patients use THC and have found an effective dose for their medical condition that does not cause psychoactivity. It may take trial and error, starting with a low dose and increasing little by little to find the "sweet spot."

Comparison of the Most Common Different Delivery Methods

inhalation	*oral ingestion*	*sublingual*	*topical*
• Onset within minutes • Peak effect in 30 minutes • Lasts 1 - 4 hours • Vaporization healthier than smoking • Easier to dose since effects felt immediately	• Onset 30 – 90 minutes • Peak effect in 2 – 3 hours • Lasts 6 – 8 hours • Difficult to dose, start with small amount, redose if no effect after 90 minutes • **THC** is changed to a stronger compound when eaten; be aware that a small amount can be very potent • No equipment needed, no odor, discreet way to medicate	• Onset 15 - 60 minutes • Peak effect in 1-2 hours • Lasts 1 - 6 hours • Available as tinctures, extracts, and dissolvable strips • No equipment needed, no odor, discreet way to medicate	• For external skin use • Apply as needed to areas of pain or rash • **CBD** absorbs better than **THC** • Repeat dose as needed • Apply a small amount to non-affected area to test for possible allergic response

Sources

Amada, Naoki, et al. "Cannabidivarin (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression." PeerJ 1 (2013): e214.

Appendino, Giovanni, et al. "Antibacterial cannabinoids from Cannabis sativa: a structure− activity study." Journal of natural products 71.8 (2008): 1427-1430.

Bolognini, D., et al. "Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation." British journal of pharmacology 168.6 (2013): 1456-1470.

Bouchard, Maryse F., et al. "Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides." Pediatrics 125.6 (2010): e1270-e1277.

Elsohly, Mahmoud A., et al. "Rectal bioavailability of Δ-9-tetrahydrocannabinol from the hemisuccinate ester in monkeys." Journal of pharmaceutical sciences 80.10 (1991): 942-945.

Englund, Amir, et al. "The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: A placebo-controlled, double-blind, crossover pilot trial." Journal of Psychopharmacology (2015): 0269881115615104.)

Formukong, E., Analgesic and anti-inflammatory activity of constituents of Cannabis sativa L. Inflammation (1988) 12: 361

Garry, Vincent F., et al. "Pesticide appliers, biocides, and birth defects in rural Minnesota." Environmental Health Perspectives 104.4 (1996): 394.

Gieringer, D., The California/MAPS Smoking Device Study, MAPS Newsletter 1996; www.canorml.org/healthfacts/smokestudy.html

Giacoppo, Sabrina, et al. "Cannabinoids: new promising agents in the treatment of neurological diseases." Molecules 19.11 (2014): 18781-18816.

Hammell, D. C., et al. "Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis." European Journal of Pain (2015).

Hayden, Kathleen M., et al. "Occupational exposure to pesticides increases the risk of incident AD The Cache County Study." Neurology 74.19 (2010): 1524-1530.

Hill, A. J., et al. "Cannabidivarin is anticonvulsant in mouse and rat." British journal of pharmacology 167.8 (2012): 1629-1642.

Hill, T. D. M., et al. "Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism." British journal of pharmacology 170.3 (2013): 679-692.

Iannotti, Fabio Arturo, et al. "Nonpsychotropic Plant Cannabinoids, Cannabidivarin (CBDV) and Cannabidiol (CBD), activate and desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability." ACS chemical neuroscience 5.11 (2014): 1131-1141.

Izzo, Angelo A., et al. "Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb." Trends in pharmacological sciences 30.10 (2009): 515-527.

Karsak, M., "Attenuation of Allergic Contact Dermatitis Through the Endocannabinoid System." Science (2007) 316: 1494-97

Laprairie, R. B., et al. "Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor." British journal of pharmacology 172.20 (2015): 4790-4805.

Mattes, Richard D., et al. "Bypassing the first-pass effect for the therapeutic use of cannabinoids." Pharmacology Biochemistry and Behavior 44.3 (1993): 745-747.

Perlin, Elliott, et al. "Disposition and bioavailability of various formulations of tetrahydrocannabinol in the rhesus monkey." Journal of pharmaceutical sciences 74.2 (1985): 171-174.

Phan, Ngoc Quan, et al. "Adjuvant topical therapy with a cannabinoid receptor agonist in facial

postherpetic neuralgia." JDDG: Journal der Deutschen Dermatologischen Gesellschaft 8.2 (2010): 88-91.

Rock, E. M., and L. A. Parker. "Effect of low doses of cannabidiolic acid and ondansetron on LiCl-induced conditioned gaping (a model of nausea-induced behaviour) in rats." British journal of pharmacology 169.3 (2013): 685-692.

Russo, Ethan B. "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects." British journal of pharmacology 163.7 (2011): 1344-1364.

Russo, Ethan B. "Current Therapeutic Cannabis Controversies and Clinical Trial Design Issues." Front Pharmacol (2016c) 7:309. doi: 10.3389/fphar.2016.00309.

Takeda, Shuso, et al. "Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis." Drug metabolism and disposition 36.9 (2008): 1917-1921.

Takeda, Shuso, et al. "Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration." Toxicology letters 214.3 (2012): 314-319.

Zuardi, A., et al. "A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation." Curr Pharm Des 18.32 (2012): 5131-40.

Elise's Story

Now 27 years old, Elise was diagnosed with Juvenile Rheumatoid Arthritis when she was 16, after a year of symptoms. She had begun having symptoms of the disease the year before. She would step off curbs while walking and notice that her heel would begin to swell. During the summer, she went bowling and noticed that not only her bowling elbow was swollen, but the other side as well. These were little clues that led to the diagnosis, but it took about a year for the symptoms to become unbearable enough that she couldn't ignore them. She began getting sicker and sicker with swelling in her knees and feet that prevented her from walking. The combination of pain and swelling caused enough nausea that she could no longer eat and began to lose weight. She was referred to a rheumatologist at a children's hospital but had to wait a couple of months for an appointment. When he finally saw her, the doctor admitted her immediately to the hospital where she stayed for one week.

Elise said, "That was the beginning of being sick and the end of being well."

In the hospital, Elise was given a myriad of medications, including steroids. The medical team told her that she would be started on biologics (strong medications that affect the immune system) and would learn over time to give the shots to herself. She and her family read over the side effects and were frightened by them, but Elise was very sick, and they felt they had no choice. At one point, a doctor told the family that the steroids shot into Elise's joints could cause calcification and fuse them. Elise had memories of her grandfather with whom she had had a special relationship as a little girl. She remembered his hands, curled and deformed. She remembered his wheelchair. She thought of him when she was diagnosed. He, too, had RA.

Despite the gravity of Elise's immediate condition and the diagnosis, the doctors were optimistic that she would go into remission. Unfortunately, Elise's response to the pharmaceuticals wasn't positive. She developed terrible side effects, and her pain increased. She was always sick and eventually couldn't walk or take care of herself. She began college but had to drop out and eventually began using a wheelchair. She grew increasingly depressed as the pain and inflammation increased. Her immune system constantly crashed and, while she tried to distract herself watching old movies, reading online and doing art with a computer app, she felt ashamed that her life was so abnormal. She told me that she was in too much pain to do anything or go anywhere. Even a trusted osteopath who had treated her for years warned Elise that she was worried about her life.

Elise's mother had been researching cannabis and wanted Elise to try it, but Elise didn't pay attention. She believed the stereotype that people using it were just stoners. When her parents began suggesting she try a new pharmaceutical

instead, she consented to come see me. Her exam showed severe deformities of her hand joints, as well as swollen knees with very poor range of motion. She had only a tiny bit of hope that day when she came in but later told me she immediately felt a connection to me and appreciated how honest I was about whether or not the cannabis would help her.

She tried different products and had mixed results at first, but in March of 2015, almost ten years after her diagnosis, she began a new CBD-rich oil and noticed a drastic difference within weeks. Before starting the oil, Elise felt so weak that she was afraid that she wouldn't make it to her beloved sister's wedding. This sister had been a support to her through all the years of Elise's illness, a best friend and the only person who Elise allowed to see how deeply the disease had affected her. She told me that the two of them would cry together, her sister begging her to hold on and be at her wedding.

Elise knew that something good was happening when she reported that one morning she felt well enough to try to move from her wheelchair to the toilet by herself. When she succeeded, she was so shocked that she called her mother into the bathroom to witness what she reported was freedom for the first time in 10 years! She had described herself as a sort of Tin Man from the "The Wizard of Oz," with fused arms and no range of motion, but within weeks of starting the oil, the swelling and inflammation in her joints was going down. She could uncurl and open her fingers and elbows.

Elise places the oil under her tongue, allowing it to dissolve in her mouth. As it's absorbed, she swears she feels her joints popping and opening. She uses both THC and CBD medicine to control both inflammation and pain. She found that she didn't like smoking or vaporizing and that the oil was more convenient and kept her medicated longer.

The effects of cannabis medicine on this young woman have been profound. Where before the most basic of activities, like bathing or showering, were so painful they were only to be dreaded, today Elise reports that she can get into and out of the tub by herself, that she can wash herself and her hair with ease. Her independence has grown tremendously, and she is now cooking for herself as well.

"I'm trying to get some normalcy in my life," she reported. "For so long, I couldn't do anything. I'm living again. I feel like this is the medicine that I prayed for, yet didn't know existed. Finding cannabis was an answer to those prayers. I am so thankful to all those who shared their stories and encouraged me to try it. Everything shared was something that gave me hope that I could have a better life."

Elise also made it to her sister's wedding in June of 2015.

CHAPTER 5
Medical Risks of Cannabis Use

I am treating patients who are seeking an effective solution to their difficult medical conditions. I rarely see major issues with cannabis use as patients are using medical doses and including CBD in their regimens. Quite simply, my patients are using cannabis as medicine, responsibly and thoughtfully.

I ask every patient if they have any side effects and the majority report that they have none. Any side effects that patients experience can often be resolved with changes in delivery method, CBD:THC ratios, chemovars or dosing.

However, studies have shown medical risks from cannabis in certain situations. These include possible increased risks to those with cardiovascular disease, pulmonary risks from smoking, risks from accidental injury while under the influence of cannabis, risks during pregnancy and breastfeeding, and risks in the pediatric population, specifically to developing brains.

It is important to understand that the studies noted here focused primarily on those using THC-rich cannabis, and that the findings listed in this chapter do not apply to CBD-rich cannabis.

Cardiovascular Risks associated with THC use

What we know about THC and its effects on the heart and blood pressure:

- THC causes an increase in heart rate within minutes of use; heart rate will return to normal after a few hours; the heart rate increases by about 20-50 beats per minute.
- THC can cause an elevation of blood pressure when one is lying flat but there is a risk of blood pressure dropping if one stands too quickly.
- Many sources cite that blood pressure decreases due to vasodilation of the blood vessels and overall relaxation with THC use.
- The cardiovascular effects of THC are more pronounced in the new or inexperienced user; regular users of THC develop a tolerance to these effects; tolerance to THC itself is not dangerous but can eventually decrease the effectiveness of the medicinal benefits.

Summary of scientific studies:

- Three studies showed a rare association with possible development of abnormal cardiac rhythms with THC use.[1,2,3]
- In one study, smoking THC-rich cannabis was related to a more rapid onset of chest pain in patients with a history of chest pain when they underwent a stress test shortly after smoking a marijuana cigarette. It's noted that this effect may be due to the carbon monoxide in the smoke as opposed to a THC effect.[4]
- One study showed an increased relative risk of developing a heart attack in the first hour after smoking marijuana (4.8 times increased risk over baseline).[5]
- There are a few case reports of young persons who have had heart attacks, arrhythmias and even cardiac arrest after using cannabis.[6,7] Note that there are only a few case reports in scientific literature and other factors such as tobacco use, alcohol use and previously unknown cardiac disease may have played a role.
- One study showed marijuana use was associated with three-fold greater mortality following acute myocardial infarction, with a graded increase in risk with more frequent use.[8]
- A recent review of the risk of cardiovascular disease (this definition included coronary artery disease, heart attack, heart failure, cardiac chest pain, and stroke) in 3,051 people revealed that marijuana use was not significantly associated with an increased risk of cardiovascular disease.[9]

It appears that there is a risk, however rare, of myocardial infarction, arrhythmias and even cardiac arrest with cannabis use. **Remember that the above findings relate to THC use, not CBD use.** The best approach in these situations is for those patients with **known cardiovascular disease** who are investigating the use of medical cannabis to discuss the scientific data available, the risks and the benefits with their personal physician, cardiologist and a knowledgeable cannabis specialist. If the decision to use medical cannabis is made, these patients should avoid smoking by choosing a different method of delivery, such as edibles or tinctures, and they should consider using CBD-rich cannabis products.

Pulmonary Risks of Smoking Cannabis

What we know about cannabis smoke:

- Cannabis smoke contains similar contents to tobacco smoke, including ammonia, hydrocyanic acid, nitrosamines, and tar components including phenols and naphthalene. Carcinogenic compounds including benzopyrene and benzanthracene are also in cannabis smoke.
- Very importantly, cannabis smoke does not contain nicotine and does contain phytocannabinoid compounds.
- Tobacco smoke causes narrowing of the airways but cannabis smoke causes bronchodilation, opening of the airways. THC has been found to be the compound causing this effect with cannabis smoke.

Summary of scientific studies:

- Smokers of tobacco only, cannabis only and smokers of both have increased incidence of respiratory symptoms, including chronic cough, phlegm production, wheezing and bronchitis when compared to non-smokers.[10,11]
- Multiple studies document that chronic cannabis smoking (without tobacco use) is associated with an increased prevalence of bronchitis.[12,13,14,15,16]
- Symptoms of chronic bronchitis from smoking cannabis alone resolve with cessation of smoking.[17]
- Studies on lung function in chronic cannabis smokers are conflicting, with some studies showing no difference from non-smokers, others showing mild airflow obstruction.[18,19,20]
- Two large studies failed to show an association between cannabis smoking and lung cancer.[21,22]
- A large study comparing 611 lung cancer cases, 601 upper airway cancer cases and 1,040 matched control subjects found no associations between cannabis use and risk of cancer; however, the study reports that the risk of cancer was clearly associated with tobacco use.[23]
- A study investigating the combined effects of tobacco and cannabis smoking revealed that smoking both tobacco and marijuana synergistically increased the risk of respiratory symptoms and COPD (chronic obstructive pulmonary disease, also called emphysema) but that smoking only marijuana was not associated with an increased risk of respiratory symptoms or COPD.[24]

In summary, it appears that chronic smokers, whether using tobacco or cannabis, have an increased risk of developing respiratory symptoms such as

chronic cough, bronchitis, wheezing and increased phlegm. Studies do not show an increased risk of cancer with cannabis smoke despite the presence of carcinogenic compounds. It has been hypothesized that the presence of cannabinoid compounds in cannabis smoke may be protective against the development of cancer but definitive research remains to be done.

To quote Dr. Donald Tashkin, a pulmonologist at UCLA and the world's leading researcher of the effects of cannabis smoke on the lungs, "the risks of pulmonary complications of regular use of marijuana appear to be relatively small and far lower than those of tobacco smoking. However, such potential pulmonary risks need to be weighed against possible benefits in consideration regarding medicinal use of marijuana."[25]

Since there are many different methods available to patients who want to use cannabis medicine, one does not have to smoke it in order to reap the benefits. In a survey of my patients, approximately 80% who switched from smoking to vaporization found excellent results and no longer smoked. Those who continue to smoke often obtain cannabis flower that is higher in potency so they can smoke less to achieve the same effect. Since sublingual and edible preparations are now regularly tested and properly labeled, they are more reliable than they have been in the past, and many patients can achieve the same medicinal benefit without smoking.

Risks of Accidental Injury with THC use

Summary of scientific studies:

- Driving simulator studies show that cannabis can adversely affect certain driving skills, in particular tracking ability, attentiveness, judgment of speed and distance, peripheral vision and coordination at complex tasks.[26,27]
- A comprehensive survey of 10 years of U.S. accident data found that alcohol-free drivers with THC in their system had a slightly elevated risk of unsafe driving behavior, but lower than that for drivers with legal amounts of alcohol in their blood.[28]
- Studies have found that THC is significantly more hazardous in the first one-two hours of acute intoxication.[29,30]
- Alcohol and THC used together increases the risk of fatal accidents.[31]
- A number of studies showed the odds of causing death or injury were slightly lower in cannabis users than in people who had not used drugs.[32,33,34,35]

- It is postulated that drivers under the influence of cannabis may have lower risks of motor vehicle accidents because of "over-compensation behavior," that is, they appear to drive slower and avoid adverse driving situations.[36]

Although the studies may be conflicting, a few things are clear. Driving while under the influence of any psychoactive drug is a bad idea. Combining cannabis with alcohol is dangerous and increases the risk of accidents. Although cannabis patients may over-compensate while driving under the influence and actually be less at risk, it is illegal to drive under the influence, and this is not advised in any circumstance.

Pregnancy and Breastfeeding with THC use

Summary of scientific studies:

- It has been reported that THC crosses the placenta and enters the circulation of the fetus, reaching concentration of 10% – 30% of the maternal concentration.[37]
- One study suggests prenatal cannabis use resulted in a decrease in fetal growth, while another study reports an increase in fetal growth, although neither controlled for socioeconomic status or use of other substances.[38,39]
- An increased incidence of preterm labor has been reported while other studies fail to find any association between preterm labor and maternal cannabis use.[40]
- A recent study found maternal cannabis use specifically was associated with a small increase of risk for aggressive behavior and attention problems in 18-month-old girls, but not boys.[41]
- Slightly reduced motor development in 1 year olds whose mothers reported smoking cannabis during breastfeeding has been reported, but no effect on mental development was noted.[42]
- In another study of 27 infants evaluated at 1 year of age who were exposed to marijuana via breast milk (compared to 35 non exposed infants), no significant differences were found in terms of age at weaning, growth, and mental or motor development.[43]
- No significant physical or psychological differences were found between three-day old newborns of heavy marijuana-using mothers and non-users in Jamaica.[44]

- A recent comprehensive review of all studies concluded that there is a subtle association between prenatal cannabis exposure and certain neurobehavioral and cognitive deficits, and these findings appear to be primarily associated with children exposed to heavy amounts of cannabis as well as alcohol and/or tobacco.[45]

As you can see, studies on maternal cannabis use during pregnancy and breastfeeding reveal conflicting results. Although it appears to be safe overall, most physicians do not recommend drug use of any kind during pregnancy or breastfeeding unless there are special circumstances such as severe morning sickness or other serious symptoms that cannot be safely treated with other medications.

By far, the largest risk I have seen as a cannabis physician is the risk of having a newborn taken away by Child Protective Services if either the mother or the newborn has a positive THC drug test during the pregnancy or at the time of birth. Cannabis use still remains controversial in general and use by pregnant women is especially frowned upon by society and the medical community.

I have been involved in a number of cases where the mother or infant tested positive for THC and the aggressiveness of social workers and the legal system is astounding, especially when the scientific literature is inconclusive. Tobacco smoking and use of alcohol during pregnancy both have significant proven risks, such as fetal alcohol syndrome, increased risk of premature birth, etc., and are not targeted by our legal system. Until society, the medical community, and legal system have an understanding of the true risks of cannabis use during pregnancy, I advise women who are pregnant not to use cannabis to avoid the devastation of having their baby removed from the family by Child Protective Services.

Risks of THC use in Pediatric Population

Human brain development and the role of the endocannabinoid system throughout childhood and adolescence has been the focus of a number of scientific studies. The adolescent brain is different from the mature adult brain in its structure and in the way it's neurotransmitters function. There is an increased sensitivity to changes and exposures in its environment, resulting in a vulnerability of the adolescent brain that is not present once the brain fully develops.

Researchers have found that endocannabinoids are crucial in influencing how neurotransmitters in the developing brain promote proper circuitry and new brain growth. The endocannabinoid system goes through necessary changes during the adolescent years, with heightened cannabinoid receptor density and possibly sensitivity. Interference with these changes, for example

the use of THC, which can over-activate the cannabinoid receptor, may interfere with the development of the mature brain.[46,47] Normal endocannabinoid system functioning during these critical years is required for emotional and cognitive functions to develop and mature correctly.[48]

One researcher summed up the importance of the endocannabinoid system in the developing brain this way, "endocannabinoid signaling is an important determinant of maturation of the adult brain … it seems quite likely that disruption of normative endocannabinoid signaling during adolescence may have long-standing consequences on adult brain function."[49]

Summary of scientific studies:

- Numerous animal studies have documented that THC or synthetic cannabinoids given to adolescent animals induce changes in emotional behavior, reward response, endocannabinoid levels, and impulsivity.[50,51,52]
- Studies in human adolescents (ages 12-18 years) who are heavy users of THC-rich cannabis have shown that the interference of the normal endocannabinoid system functioning may result in some long-lasting brain changes that may be deleterious, especially in the areas of emotional and mental illness (especially anxiety disorders), impulsivity control, memory issues, attention, decision-making and lowered overall and verbal IQ. First time cannabis use after the age of 18 years was not associated with lowered IQ or neurocognitive performance.[53,54]
- Although schizophrenia does not develop in the majority of teenagers that use cannabis, those with increased risk factors, such as schizophrenia or mental illness in a family member and chronic heavy cannabis use at a young age, have an increased risk of developing schizophrenia as a young adult.[55,56,57]

As a pediatrician, medical cannabis specialist and the mother of a teenager, I am strongly opposed to **healthy or otherwise "typically" developing** children and adolescents using cannabis. I am also opposed to cannabis use (and pharmaceutical use) in children and adolescents with mild illnesses, such as occasional anxiety or sleep disturbance, as other treatment modalities (talk therapy, exercise, proper diet, sleep hygiene, etc.) can and should be used in these instances. However, children and adolescents with moderate to severe medical conditions that either significantly disrupt quality of life or are life-threatening or life-limiting should absolutely have the option of using cannabis under medical supervision.

Sources

[←1]

Fisher, B. A. C., et al. "Cardiovascular complications induced by cannabis smoking: a case report and review of the literature." *Emergency medicine journal* 22.9 (2005): 679-680.

[←2]

Kosier, D., et al. Paroxysmal Atrial Fibrillation Following Marijuana Intoxication: A Two-case Report of Possible Association. *International Journal of Cardiology* (2001) 78: 183-84

[←3]

Singh, G. Atrial Fibrillation Associated with Marijuana Use. *Pediatric Cardiology* (2000) 21: 248

[←4]

Aronow, W., et al. Effect of Marihuana and Placebo-marihuana Smoking on Angina Pectoris. *New England Journal of Medicine* (1974) 291: 65-67

[←5]

Mittleman, M., et al. Triggering Myocardial Infarction by Marijuana. *Circulation.* (2001) 103:2805

[←6]

Fisher, B. A. C., et al.

[←7]

Caldicott, D., et al. Keep off the grass: marijuana use and acute cardiovascular events. *European Journal of Emergency Medicine* (2005) 12: 236-244

[←8]

Mukamal, K. An Exploratory Prospective Study of Marijuana Use and Mortality Following Acute Myocardial Infarction. *American Heart Journal* (2008) 155: 465-470

[←9]

Axiyan, Maihemuti, et al. "CardiovasculaR Disease among us adult marijuana users: National Health and Nutrition Examination Survey, 2011-2012." *Journal of the American College of Cardiology* 65.10_S (2015).

[←10]

Tashkin, Donald P., et al. "Respiratory Symptoms and Lung Function in Habitual Heavy Smokers of Marijuana Alone, Smokers of Marijuana and Tobacco, Smokers of Tobacco Alone, and Nonsmokers 1–3." *American Review of Respiratory Disease* 135.1 (1987): 209-216.

[←11]

Bloom, John W., et al. "Respiratory effects of non-tobacco cigarettes." *BMJ* 295.6612 (1987): 1516-1518.

[←12]

Tashkin, Donald P., et al.

[←13]

Bloom, John W., et al.

[←14]

Aldington, Sarah, et al. "Effects of cannabis on pulmonary structure, function and symptoms." *Thorax* 62.12 (2007): 1058-1063.

[←15]

Taylor, D. Robin, et al. "The respiratory effects of cannabis dependence in young adults." *Addiction* 95.11 (2000): 1669-1677

[←16]

Moore, Brent A., et al. "Respiratory effects of marijuana and tobacco use in a US sample." *Journal of General Internal Medicine* 20.1 (2005): 33-37.

[←17]

Tashkin, Donald P., Michael S. Simmons, and Chi-Hong Tseng. "Impact of changes in regular use of marijuana and/or tobacco on chronic bronchitis." *COPD: Journal of Chronic Obstructive Pulmonary Disease* 9.4 (2012): 367-374.

[←18]

Tashkin, Donald P., et al.

[←19]

Aldington, Sarah, et al.

[←20]

Hancox, Robert J., et al. "Effects of cannabis on lung function: a population-based cohort study." *European Respiratory Journal* 35.1 (2010): 42-47.

[←21]

Sidney, Stephen, et al. "Marijuana use and cancer incidence (California, United States)." *Cancer Causes & Control* 8.5 (1997): 722-728.

[←22]

Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM,Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. Am. J. Respir. Crit. Care Med. 1997;156: 1606–13

[←23]

Hashibe, Mia, et al. "Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study." *Cancer Epidemiology Biomarkers & Prevention* 15.10 (2006): 1829-1834.

[←24]

Tan, Wan C., et al. "Marijuana and chronic obstructive lung disease: a population-based study." *Canadian Medical Association Journal* 180.8 (2009): 814-820.

[←25]

Tashkin, Donald P. "Effects of marijuana smoking on the lung." *Annals of the American Thoracic Society* 10.3 (2013): 239-247.

[←26]

Tunbridge, R. J., et al. *The influence of cannabis on driving*. Crowthorne: Transport Research Laboratory, 2000

[←27]

Smiley, Alison M., H. Moskowitz, and K. Zeidman. "Driving simulator studies of marijuana alone and in combination with alcohol." *Proceedings: American Association for Automotive Medicine Annual Conference*. Vol. 25. Association for the Advancement of Automotive Medicine, 1981.

[←28]

Bedard, M., et al. The impact of cannabis on driving. *Canadian Journal of Public Health* (2007) 98: 6-11

[←29]

Drummer, O., et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accident Analysis and Prevention* (2004) 36: 239-48

[←30]

Grotenhermen, F., et al. Developing science-based per se limits for driving under the influence of cannabis. **http://www.canormL.org/healthfacts/DUICreport2005.pdf** (2005)

[←31]

US Department of Transportation, National Highway Traffic Safety Administration. *The Incidence and Role of Drugs in Fatally Injured Drivers: Final Report*, October 1992

[←32]

Drummer, O., et al.

[←33]

The Incidence and Role of Drugs in Fatally Injured Drivers: Final Report, October 1992

[←34]

Williams, A., et al. Drugs in Fatally Injured Young Male Drivers. *Public Health Reports* (1985) 100: 19-25

[←35]

Bates, M., Role of cannabis in motor vehicle crashes. *Epidemiological Reviews* (1999) 21:222-232

[←36]

Drummer, O., et al.

[←37]

Grotenhermen, F., Pharmacokinetics and Pharmacodynamics of Cannbinoid. *Clinical Pharmacokinetics* (2003) 42: 327-60

[←38]

Fried, P., et al. A Literature Review of the Consequences of Prenatal Marijuana Exposure: An Emerging Theme of a Deficiency in Aspects of Executive Function. *Neurotoxicology and Teratology* (2001) 23: 1-11

[←39]

Hurd, Y., et al. Marijuana Impairs Growth in Mid-gestation Fetuses. *Neurotoxicology and Teratology* (2005): 221-29

[←40]

Fried, P., et al

[←41]

Marroun H., et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. *Drug and Alcohol Dependence* (2011) April

[←42]

Astley S., et al. Maternal marijuana use during lactation and infant development at one year. *Neurotoxicology and Teratology* (1990) 12:161-168

[←43]

Tennes, K., et al. Marijuana: Prenatal and Postnatal Exposure in the Human. In T. M. Pinkert (ed.), *Current Research on the Consequences of Maternal Drug Abuse* (Rockville, MD: National

Institute on Drug Abuse, 1985) pg 48–60

[←44]

Dreher et al. 1994. Prenatal marijuana exposure and neonatal outcomes in Jamaica: An ethonographic study. *Pediatrics* 93: 254-260.

[←45]

Huizink, Anja C., and Eduard JH Mulder. "Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring." *Neuroscience & Biobehavioral Reviews* 30.1 (2006): 24-41.

[←46]

Lee, TT-Y., and B. B. Gorzalka. "Timing is everything: evidence for a role of corticolimbic endocannabinoids in modulating hypothalamic–pituitary–adrenal axis activity across developmental periods." Neuroscience 204 (2012): 17-30.

[←47]

Chadwick B, Miller ML, Hurd YL. Cannabis use during adolescent development: susceptibility to psychiatric illness. Front Psychiatry. 2013;4:129

[←48]

Díaz-Alonso, Javier, Manuel Guzmán, and Ismael Galve-Roperh. "Endocannabinoids via CB1 receptors act as neurogenic niche cues during cortical development." *Philosophical Transactions of the Royal Society B: Biological Sciences* 367.1607 (2012): 3229-3241.

[←49]

Malone, Daniel T., Matthew N. Hill, and Tiziana Rubino. "Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models." *British journal of pharmacology* 160.3 (2010): 511-522.

[←50]

Rubino, Tiziana, et al. "Chronic Δ9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates." *Neuropsychopharmacology* 33.11 (2008): 2760-2771.

[←51]

Rubino, T., and D. Parolaro. "Long lasting consequences of cannabis exposure in adolescence." *Molecular and cellular endocrinology* 286.1 (2008): S108-S113.

[←52]

Trezza, Viviana, and Louk JMJ Vanderschuren. "Bidirectional cannabinoid modulation of social behavior in adolescent rats." *Psychopharmacology* 197.2 (2008): 217-227.

[←53]

Renard, Justine, et al. "Long-term consequences of adolescent cannabinoid exposure in adult psychopathology." *Frontiers in neuroscience* 8 (2014).

[←54]

Meier, M.H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R.S., et al., 2012. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc. Natl Acad. Sci. USA 109 (40), E2657E2664.

[←55]

Sugranyes, Gisela, et al. "Cannabis use and age of diagnosis of schizophrenia." *European psychiatry* 24.5 (2009): 282-286.

[←56]

Arseneault, Louise, et al. "Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study." *Bmj* 325.7374 (2002): 1212-1213.

[←57]

Stefanis, N. C., et al. "Early adolescent cannabis exposure and positive and negative dimensions of psychosis." *Addiction* 99.10 (2004): 1333-1341.

Kiana's Story

When Nazy and her daughter Kiana walked into my office recently, I couldn't believe I was seeing the same child I met two years ago. When they initially came to my office, Kiana had already been on cannabis oil for a few months to treat her seizures, but her parents were frustrated by inconsistent results. They had seen some improvement with CBD but they were exhausted with the constant chaos her medical conditions and the side effects the medications were causing.

Nazy and her husband live in the San Fernando Valley with their only child, now eleven-year old daughter Kiana. When Kiana was born, the doctors suspected she had hypochondroplasia (a type of dwarfism), but it wasn't a definitive diagnosis and it soon became evident that the baby had additional significant issues. At three days old, she was diagnosed with congenital hypothyroidism and immediately put on thyroid medication. Nazy remembers spending weeks in the hospital filled with anguish over what was unfolding as her baby underwent genetic testing that was inconclusive. Eventually, Kiana went home and at four months old received her first vaccinations. That evening, Nazy noticed what looked to be a seizure, but her doctor assured her that it was unlikely and unrelated to the vaccinations. Nazy believes that the doctors were used to her panicking and therefore dismissed her fears about seizure, and it wasn't until Kiana was nine months old that the doctor agreed that the baby was experiencing seizures.

The family's life changed, Nazy told me, when Kiana went into a long uncontrollable seizure (called status epilepticus) one morning while Nazy was driving. After calling 911, Kiana was transported to the hospital and admitted to the intensive care unit. Over the next three years she would be hospitalized multiple times, each time in status epilepticus. The only way the doctors could stop her seizures was to induce a coma, despite multiple treatment with multiple medications. By age 9, Kiana had tried 14 different drugs and combinations, all of which gave her terrible side effects, particularly behavioral. Nazy suspected her daughter's extreme hyperactivity, disruptive behavior, head-banging, screaming and refusal to eat were due to the anticonvulsants she was taking, but her doctors dismissed her ideas and told her Kiana was a "very complex kid." Genome sequencing did not reveal any specific diagnosis so the family was told Kiana had a refractory seizure disorder and hypochondroplasia. Brain surgery was recommended in lieu of other treatments.

Nazy was concerned about the possible risks with brain surgery and wanted to think about it before agreeing, so during the pre-testing and despite the neurologists' conviction that there were no other options, she started

researching alternative medicine and came across some articles about cannabis. Just when the hospital called to make a date for the surgery, Nazy insisted that she and her husband did not want the surgery and would try something different first. The doctors were upset with her, but she persisted. Around the same time the CNN documentary "Weed" aired with the story of Charlotte, a little girl in Colorado whose life-threatening and uncontrollable seizure disorder was finally controlled with CBD oil. "I decided this was IT," Nazy said.

Ready to move to Colorado to try cannabis, Nazy discovered that she could obtain CBD oil in California. She started Kiana on the oil in August of 2013. Within one week, her daughter's behavior changed. She became calmer. Within two months, her seizures lessened in both severity and duration. During the first six months, Kiana was weaned off one of her seizure medications and her parents saw even more improvement in both behavior and seizures. While she continues to take medication for her hypothyroidism, her thyroid levels stabilized, where they were once quite varied.

Kiana's quality of life and that of her family improved so dramatically that it still feels almost unbelievable to Nazy and her husband. Despite years of speech therapy, Kiana was largely non-verbal, but within two months of taking cannabis medicine, she began talking. Nazy could leave the house with Kiana and take her on outings to the grocery store, to coffee shops and restaurants without seizures, meltdowns and disruption. The head banging and screaming stopped. She began eating again and even started feeding herself. Over the next eighteen months, her comprehension and alertness improved dramatically and, equally as important, she had long periods of seizure freedom. Her teachers and therapists are amazed by her progress and accomplishments. Nazy never imagined that Kiana would be able to read or write, and in that recent follow-up visit to my office, Kiana proudly wrote her full name and read a book to me.

"The quality of our life is astounding," Nazy told me that day in my office. "Kiana was like a zombie before and I'd given up hope."

Kiana is being weaned off the second anticonvulsant and continues to show amazing progress at school and at home. She is living a good life. Her family can't imagine a day without cannabis medicine.

CHAPTER 6
Medical Symptoms and Conditions

The designation of cannabis as a Schedule I Controlled Substance has impeded research, but the discovery of the endocannabinoid system over two decades ago has triggered a recent explosion of scientific investigation into cannabis as medicine. While scientists have learned a tremendous amount from this research, it is my patients' experiences that have truly informed me about medical cannabis.

In the following section, I have reviewed the scientific literature for each condition as it relates to cannabis. Some illnesses have been studied in depth, while others have not been studied at all. The variables in studying cannabis and the endocannabinoid system are almost too many to count. Much of the research used synthetic THC, which is quite different from natural whole plant cannabis. Some of the research used an orally administered THC, which has erratic absorption and significant individual differences in effects, due to the wide variation of metabolism from person to person. Research on the effects of CBD often uses the isolated CBD molecule that is difficult to compare to CBD-rich chemovars that contain other cannabinoids and terpenoids. With this single molecule treatment, the entourage effect is lost. Although animals have endocannabinoid systems, it is difficult to use them as a comparison to human physiology. If patients recruited into a study have varying endocannabinoid system dysfunction (or lack of dysfunction), the outcome of the study may also be skewed in a certain direction.

All of these factors must be taken into account when using research to decide if you should use cannabis. I find that patient experience often does not reflect the conclusions reached in studies, probably due to the variables I've mentioned above. Although I see people with many different conditions in my office, I find a thread of commonality among many of them.

Chronic illnesses that prompt a patient to seek out medical cannabis treatment have very similar basic symptoms – chronic pain, disruption of sleep, anxiety, depression and inability to participate in life – all of which are treated effectively with cannabis.

Although most conditions are not cured with cannabis, managing and sometimes eliminating these symptoms with a non-toxic natural medicine

allows patients to experience an improved quality of life that is not controlled by illness. Being able to participate in life, at home and at work, as well as the elimination of suffering is what my patients report to me every single day.

Cannabis is medicine.

Analgesia/Pain Relief

Cannabis has been documented as an effective pain reliever for thousands of years. In a review of patients seeking cannabis therapy in California in 2006, 82.6% of applicants reported using cannabis for pain relief. The majority of these patients had tried prescription pharmaceuticals, physical therapy, surgery, acupuncture and/or chiropractic therapy prior to seeking cannabis treatment through a physician.[1]

Many patients who are suffering with chronic pain report having less pain and better quality of life with the use of medicinal cannabis. I have seen thousands of patients with arthritis, neuropathy, post-traumatic or post-surgical pain, chronic back pain and other pain conditions reduce or discontinue use of pharmaceutical pain medications including NSAIDS and opiates. My patients report over and over that when pain is controlled, sleep is better, anxiety is reduced, and functioning at home and at work is vastly improved.

In terms of published research, patients with cancer pain using cannabis have been the most studied group of pain patients, followed by those suffering from neuropathic pain. The studies assessing the analgesic effects of cannabis and the cannabinoids are summarized here:

- Smoked cannabis produced significant dose-dependent pain relief in a randomized, double-blind, placebo controlled study.[2]
- A statistically significant increase in pain tolerance was observed after use of smoked cannabis in a placebo-controlled study.[3]
- In a randomized, double-blinded, placebo-controlled crossover trial, investigators evaluated effects of low-, medium-, and high-dose smoked cannabis on pain and cutaneous hyperalgesia induced by intradermal capsaicin. There was a significant decrease in pain with the medium dose and a significant increase in pain with the high dose. There was no effect seen with the low dose, nor was there an effect on the area of hyperalgesia at any dose.[4]
- Reported results of a study looking at oral THC in various dosages showed significantly better pain relief with the higher doses versus placebo. However, these doses also produced confusion and sedation.[5]
- The same investigators compared oral THC with codeine and found that both medications were equally analgesic.[6]

- A synthetic cannabinoid (CT-3) was compared to placebo in patients with neuropathic pain. CT-3 was found to provide significant pain relief at three hours compared to the placebo, with less of a response at eight hours.[7]
- A sublingual spray of THC alone or mixed with cannabidiol was evaluated on patients with neuropathic pain with small but significant improvements in pain as well as quality of sleep.[8]
- The only study on the use of inhaled cannabis in neuropathic pain showed that patients reported significant reduction in pain when compared to the placebo (34% reduction of pain with cannabis versus 17% with the placebo), with minimal side effects.[9]
- Sativex, a sublingual spray containing equal parts THC and cannabidiol (CBD), was compared to a placebo in rheumatoid arthritis patients. Sativex produced significant pain relief with movement and at rest, and improved the quality of sleep.[10]
- Sublingual spray containing THC alone, cannabidiol alone, a combination of the two and a placebo were given to patients with chronic pain from various causes. Patients taking THC alone and THC with CBD indicated significant improvement on pain when compared to the placebo. All three medications were shown to improve quality of sleep over the placebo.[11]
- A 2015 report from Israel on cannabis patients with cancer documented that 70% of cancer patients reported pain relief with cannabis use.[12]
- A 2015 review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain found that 64% demonstrated significant pain relief from the effects of cannabis and several studies demonstrated improvement in sleep, muscle stiffness and spasticity. Side effects such as fatigue and dizziness were mild to moderate and generally well tolerated.[13]

Patients with pain from inflammatory conditions can find relief from CBD-rich medicine, THC-rich medicine or combination CBD-THC medicine. I encourage this group of patients to include some CBD in their treatment regimen since CBD is a potent anti-inflammatory. Patients with nerve-based pain (neuropathy) appear to benefit from the combination of CBD and THC in a 1:1 ratio, although some report 2:1 or 4:1 to be more beneficial. Patients who are new or inexperienced with cannabis and who

do not want psychoactivity, often start treatment with higher CBD:THC ratios, such as 25:1 down to 18:1. If they do not find relief, they will try cannabis with lower ratios such as 10:1 down to 1:1. Every person must use trial and error to find his or her “sweet spot” where symptoms improve or abate. Some patients will take higher CBD:THC ratio during the day to control daytime pain and higher THC at night to help promote sleep.

Sources

[←1]

Nunberg, Helen, et al. "An analysis of applicants presenting to a medical marijuana specialty practice in California." Journal of drug policy analysis 4.1 (2011).

[←2]

Greenwald, M., et al. Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug and Alcohol Dependence* (2000) 59: 261-275

[←3]

Milstein, S., et al. Marijuana-produced changes in pain tolerance. Experienced and non-experienced subjects. *International Pharmacopsychiatry* (1975) 10: 177-82

[←4]

Wallace, M., et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology* (2007) 107: 785-96

[←5]

Noyes, Jr., R., et al. The Analgesic Properties of Delta-9-tetrahydrocannabinol and Codeine. *Clinical Pharmacology and Therapeutics* (1975a) 18: 84-89

[←6]

Noyes, Jr., R., et al. Analgesic Effect of Delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* (1975b) 15: 139-43

[←7]

Karst, M., et al. Analgesic Effect of the Synthetic Cannabinoid CT-3 on Chronic Neuropathic Pain. *Journal of the American Medical Association* (2003) 290: 1757-62

[←8]

Berman, J., et al. Efficacy of Two Cannabis Based Medicinal Extracts for Relief of Central Neuropathic Pain from Brachial Plexus Avulsion: Results of a Randomised Controlled Trial. *Pain* (2004) 112: 299-306

[←9]

Abrams, D., et al. Cannabis in Painful HIV-associated Sensory Neuropathy: A Randomized Placebo-controlled Trial. *Neurology* (2007) 68: 515-21

[←10]

Blake, D., et al. Preliminary Assessment of the Efficacy, Tolerability and Safety of a Cannabis-

based Medicine (Sativex) in the Treatment of Pain Caused by Rheumatoid Arthritis. *Rheumatology* (2006) 45: 50-52

[←11]

Notcott, W., et al. Initial Experiences with Medicinal Extracts of Cannabis for Chronic Pain: Results from 34 'N of 1" Studies. Anaesthesia (2004) 59: 440-52

[←12]

Waissengrin, Barliz, et al. "Patterns of use of medical cannabis among Israeli cancer patients: A single institution experience." *Journal of pain and symptom management* 49.2 (2015): 223-230.

[←13]

Lynch, M. E., and Mark A. Ware. "Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials." *Journal of Neuroimmune Pharmacology* (2015): 1-9.

Dennis's Story

I met Dennis in 2009 when he came to my office seeking help with neuropathy caused by HIV medications. An older gentleman in his mid-60's with a thin build, Dennis shared that he was one of the first people to be infected with the HIV virus. He had participated in a study for a hepatitis vaccine in 1981 and had a blood sample drawn that was stored by the researchers for future investigations. A few years later, when the researchers were testing the blood, he was notified that he was infected with HIV. Although not ill at the time, he was started on two medications as physicians worried that he could develop AIDS. After a few months on these drugs, he developed severe nerve pain, called neuropathy, in both feet. Knowing that neuropathy was a serious side effect, his physicians immediately switched him to another drug regimen and reassured him that the symptoms would resolve. Unfortunately the pain has never gone away.

Dennis tried many different modalities over the next twenty years to combat the severe pain and numbness that he experiences daily. Acupuncture, multiple nerve medications, massage and even an electrical stimulator device were only somewhat effective. At times he could barely stay in bed at night as he suffered excruciating pain when the bedsheets touched his feet. The persistent pain and lack of sleep created anxiety. He had difficulty concentrating at work, which added more stress to his life. He felt hopeless, caught in a vicious cycle that could not be broken. One night while sharing his struggles with a friend at a dinner party, someone mentioned cannabis might help with the pain of neuropathy and, knowing he had exhausted all other options, he decided to try it. He found that it broke the cycle by alleviating the pain and allowing him to sleep through the night. After years of suffering, he had finally found relief.

Currently Dennis is in excellent health despite his medical conditions. After retiring from the business world, he became a certified yoga instructor and practices transcendental meditation. He finds use of THC-rich cannabis through a vaporizer on the nights when pain is bothering him allows him to sleep uninterrupted. He reports less pain and better sleep from cannabis has given him a much improved quality of life. He is now in control of the pain that used to control him.

Appetite Stimulation

Cannabis use has long been associated with an increase in appetite, often called "the munchies." Joking aside, a number of studies done in the 1970s and 1980s showed that subjects given THC had increased intake of food, primarily snack foods if people were given a choice.[1,2] Scientific research shows that cannabinoid receptors play a role in food consumption and, by activating these receptors, hunger may result.[3,4] Synthetic cannabinoids (such as dronabinol) have been shown in studies to enhance appetite, cause weight gain and stabilize body weight in AIDS patients.[5]

I have evaluated thousands of patients for the use of medical cannabis and many patients report increased appetite as one of the many benefits, although not every patient feels this effect. Poor appetite may result from cancer treatment, side effects of medication, severe anxiety and/or depression, gastrointestinal conditions and anorexia nervosa. Being able to feel hunger and have an interest in and enjoy food is normal for humans. It can be quite depressing when you can't eat and enjoy food. Cannabis can restore these feelings and can enhance quality of life for these patients.

In a previous chapter we learned that THC binds to the cannabinoid receptors in our brains, but that CBD does not act directly at these receptors. What I have found in my medical practice is that many who use THC feel hunger and report that food tastes exceptionally good. My patients using CBD do not report the same feelings of hunger with its use. This makes sense because THC and CBD work differently in the brain. However, chronically ill patients, such as those patients with severe epilepsy, report that overall appetite is enhanced when CBD is used on a regular daily schedule. This is thought to be due to the fact that when your endocannabinoid system becomes stabilized, basic human functions, such as sleeping and eating, become more balanced.

If you are a patient who has unwanted hunger with the use of cannabis, there are a few things that you can do to try to avoid or control this effect. The first thing to try is to switch the chemovar of cannabis that you are using as different chemovars can have different effects on hunger. If this doesn't work, you should assure yourself that you are not really hungry and that the sensation of hunger is just a side effect of the cannabis medication. Drinking water and eating healthy snacks, such as apples or carrots, will help curb your appetite. Some patients have found that adding CBD to their cannabis regimen can lower appetite stimulation. The best advice is to not have unhealthy snacks in your house. If they aren't there, you can't eat them!

If you are worried about gaining weight with cannabis use, the results of a

study done in 2013 should put your mind at ease. Researchers found that "the prevalence of obesity is paradoxically much lower in cannabis users as compared to non-users, and this difference is not accounted for by tobacco smoking status and is still present after adjusting for variables such as sex and age."[6,7]

Sources

[←1]

Hollister LE. Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine. Clin Pharmacol Ther 1971; 12: 44–49.

[←2]

Foltin, Richard W., Marian W. Fischman, and Maryanne F. Byrne. "Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory." *Appetite* 11.1 (1988): 1-14.

[←3]

Herkenham, M. A. B. L., et al. "Cannabinoid receptor localization in brain." *Proceedings of the national Academy of sciences* 87.5 (1990): 1932-1936.

[←4]

Williams, Claire M., Peter J. Rogers, and Tim C. Kirkham. "Hyperphagia in pre-fed rats following oral Δ 9-THC." Physiology & Behavior 65.2 (1998): 343-346.

[←5]

Beal, Jeffrey E., et al. "Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS." *Journal of pain and symptom management* 10.2 (1995): 89-97.

[←6]

Le Foll, Bernard, et al. "Cannabis and Δ 9-tetrahydrocannabinol (THC) for weight loss?." Medical hypotheses 80.5 (2013): 564-567.>

[←7]

Di Marzo, V. "The endocannabinoid system in obesity and type 2 diabetes." *Diabetologia* 51.8 (2008): 1356-1367.

ADD/ADHD

I see many patients in my office who have been diagnosed with Attention Deficit Disorder and/or Attention Deficit Hyperactivity Disorder. They report that certain chemovars of cannabis help with focus, improve concentration, and help them finish tasks. Obviously this is not the effect of cannabis on everyone, but you must remember that people diagnosed with ADD/ADHD have been found to have neurotransmitter dysfunction involving dopamine, norepinephrine and/or choline.[1] Recent evidence has also found that these patients have a genetically based endocannabinoid system dysfunction.[2] Many people with ADD/ADHD can find relief from their symptoms by targeting the dysfunctional endocannabinoid system with plant cannabinoids. The result is balanced neurotransmitters.

Conventional ADD/ADHD medications target dopamine (stimulants) or norepinephrine (non-stimulants); there are no approved medications that target choline. These medications, although effective for some, can have side effects of poor appetite, insomnia, high blood pressure, weight loss, tics, headache and stomach upset. In my experience, some patients find that cannabis by itself is very effective in treating the symptoms of ADD/ADHD. Other patients find that cannabis treatment works best by counteracting the unwanted side effects of their prescription ADD/ADHD medications, which are otherwise effective.

Many patients report that stimulating THC-rich chemovars (often referred to as Sativa) and those that contain higher amounts of pinene, a terpenoid that helps to increase focus and aids in memory, work well for ADD/ADHD sufferers. For some, the less stimulating chemovars work better, especially if they are trying to combat co-existing symptoms such as insomnia and anxiety. I encourage adult patients to try different THC-rich products to find those that work the best for them. As mentioned before, finding the correct chemovar for a particular patient usually requires a "trial and error" approach.

I have found that some pediatric patients with severe ADD/ADHD have good results with CBD-rich cannabis. Many of these patients have other diagnoses such as seizure disorders, Tourette syndrome or severe anxiety (these conditions are due to the same neurotransmitters that are imbalanced) that also improve with CBD treatment. Some children do well with higher CBD:THC ratios (for example 25:1) and others show improvement with lower ratios. Due to concerns of THC use in the developing brain, my approach for children and teenagers with severe ADD/ADHD symptoms is to start with high CBD:THC ratio preparations, assess response, and add THC in small amounts for desired effects.

Sources

[←1]

Centonze, D., et al. "Altered anandamide degradation in attention-deficit/hyperactivity disorder." *Neurology* 72.17 (2009): 1526-1527.

[←2]

Lu, Ake T., et al. "Association of the cannabinoid receptor gene (CNR1) with ADHD and post-traumatic stress disorder." American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 147.8 (2008): 1488-1494.

John's Story

When he first came to see me at the age of 19, John's mother accompanied him to the office. I noticed immediately and was touched by the close relationship between the two. John had been diagnosed with Attention Deficit Disorder when he was 11 years old after the school reported to his parents that he was struggling with schoolwork and impulsivity in the classroom. He was prescribed a stimulant medication and remembers feeling terrible on it. "I felt like a zombie," he told me. His mother also disliked the effects of the medication and stopped giving it to him, saying that it made his personality disappear. Reluctant to try other medications, she pulled him out of school and homeschooled him until John graduated from high school.

Despite being nervous that he might fail, he started college and was introduced to cannabis recreationally by some new friends. He was shocked to find that, for the first time, he was able to actually focus on schoolwork. Impulsivity, which had been a big issue for him, disappeared. He says that his brain always felt like it was racing and using cannabis had slowed his thoughts to a "normal" pace. He was able to think and process information better than he ever had.

Since John felt that cannabis was helping him achieve in school, he decided to tell his mother. Initially upset, she researched cannabis use for ADD and was surprised to learn that many people had found the same results. She made a deal with him that if his grades were good for the semester, she would take him to get his medical cannabis approval so that he could obtain and use cannabis legally and have assistance from a doctor to help him understand the best way to use it. He made straight A's that semester!

John's mother reported to me how skeptical she had been, but that she was open to cannabis treatment because he had struggled for so long. When he was first diagnosed with ADD, she shared that he felt stupid because his teachers were frustrated by his behaviors and treated him differently than the other children in the classroom. With homeschooling and individual attention, he excelled, but she was concerned about his ability to function outside of the home. Seeing him achieve in college with the responsible use of cannabis medicine assured her that he would be able to make it on his own. She is amazed and troubled that she never heard from other parents or John's doctors that cannabis could help her son combat his ADD symptoms without any side effects.

John reports that he uses THC-rich cannabis in a portable vaporizer. He drives to school in the morning and takes two to three puffs prior to his classes. He states he does not feel high. He describes the effects of cannabis as,

"my mind is calm and I can focus on learning." By the time he drives home hours later, the effects have worn off. He takes another dose when he sits down to do schoolwork. He skips cannabis on the days he is not doing schoolwork to avoid developing tolerance. He has become interested in learning about the various chemovars and terpenoids, using a trial and error approach to find the chemovars that work best for his symptoms.

John has continued to achieve and will be graduating from college next semester. He is nervous but excited to find a job and become fully independent. Concerned that many employers still drug test for THC as a drug of abuse, he is worried that he may have to stop his medicine in order to find employment. He is thinking about working in the cannabis industry as he is passionate about how profoundly cannabis medicine has changed his life and wants to change the stigma that is still associated with it.

I am proud of John, a young man who had the courage to seek out the answers to make his life better and to share it with his mother, his biggest champion.

ALS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive motor neuron loss, paralysis and death within 2–5 years of diagnosis. Also called Lou Gehrig's Disease, there is currently no treatment for this devastating disease.

The cause of ALS is unknown, but it is thought to be a result of damage to motor neurons by a nervous system gone haywire. There are a number of theories as to the possible causes of ALS, including autoimmune disease (the body's immune system attacks the brain cells and kills them), chemical imbalance of a neurotransmitter (the neurotransmitter glutamate builds up and is toxic to neurons) or abnormal accumulation of protein (which kills brain cells).

Since phytocannabinoids are anti-inflammatory and have been shown to delay the progression of neurodegenerative disease in mice, recent research has looked at how cannabinoids may help in ALS. Type 2 cannabinoid receptors were found to be increased in motor neurons in mice with a type of "mice ALS."[1] When these mice were given injections of synthetic cannabinoid targeting the type 2 cannabinoid receptors, their survival time was increased.[2],[3],[4] These findings are promising, but more research is warranted to determine which cannabinoids and what doses would be most effective in delaying damage and potentially halting ALS progression.

Many patients suffering with ALS have poor quality of life with pain, muscle spasms, wasting, trouble breathing, drooling, insomnia, anxiety and depression. Cannabis can help all of these symptoms as it works as a pain reliever, muscle relaxant, appetite stimulant, bronchodilator (opens up the lungs), sleep and mood enhancer. Because it causes drying of the mouth, it also helps with excess drooling and secretions. I have successfully treated patients with ALS who have reported improved quality of life as their debilitating symptoms are lessened. These patients found good results with THC-rich cannabis delivered by vaporizer, edibles or sublingual tinctures. Some ALS patients may also choose to add CBD to their regimen to help with spasticity and mood.

Sources

[←1]

Zhao, Pingwei, et al. "Altered presymptomatic AMPA and cannabinoid receptor trafficking in

motor neurons of ALS model mice: implications for excitotoxicity." *European Journal of Neuroscience* 27.3 (2008): 572-579.

[←2]

Kim, Kathline, et al. "AM1241, a cannabinoid CB 2 receptor selective compound, delays disease progression in a mouse model of amyotrophic lateral sclerosis." *European journal of pharmacology* 542.1 (2006): 100-105.

[←3]

Shoemaker, Jennifer L., et al. "The CB2 cannabinoid agonist AM-1241 prolongs survival in a transgenic mouse model of amyotrophic lateral sclerosis when initiated at symptom onset." Journal of neurochemistry 101.1 (2007): 87-98.

[←4]

Raman, Chandrasekaran, et al. "Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid." *Amyotrophic Lateral Sclerosis* 5.1 (2004): 33-39.

Alzheimer's Disease

Alzheimer's disease is a chronic neurodegenerative disorder that affects millions of people worldwide. Symptoms include memory loss, problems with language, disorientation, mood swings, and difficulty managing activities of daily living. About 70% of cases are thought to be genetic in cause. Researchers have found that the brains of people with Alzheimer's disease have abnormal deposits called myeloid plaques and neurofibrillary tangles. These plaques and tangles disrupt the brain cells' ability to function properly and lead to cell death, which subsequently leads to the terrible symptoms of Alzheimer's. It has also been reported that this condition may result from years of inflammation of the nerves in the brain.

Cannabinoids are well known to be potent anti-inflammatory compounds and have been shown in multiple studies to decrease neuroinflammation. Research investigating the use of cannabinoids for Alzheimer's are summarized:

- Studies show that THC blocks the formation of the plaques and tangles.[1],[2],[3],[4]
- Researchers concluded that THC in low doses "simultaneously treats both the symptoms and progression of Alzheimer's disease."[5]
- CBD exerted a combination anti-inflammatory, antioxidant and cell-saving effect from the damage that plaques and tangles cause in the brain.[6]
- Treatment of mice with Alzheimer's type disease with a combination of both THC and CBD preserved memory and decreased learning impairment.[7]

One of the main concerns involved in deciding to treat patients with Alzheimer's disease with cannabis is that THC itself can cause memory loss, disorientation, agitation and anxiety in some people. It is therefore recommended that if THC is to be used, it should be used in very small doses and titrated up very slowly. Chemovars rich in the terpenoid myrcene are sedating and can be helpful for agitated Alzheimer's patients. Sublingual tinctures that are tested for potency and that contain small amounts of THC allow for controlled dosing and prevention of unwanted side effects. However, it appears from recent research that combination treatment with CBD plus THC had better results in mice than either compound alone.

Since it has been shown that CBD can protect from memory loss[8,9,10] and can counteract the anxiety and paranoia that can occur in some who take THC,[11] it would be helpful to include CBD in any cannabis treatment for Alzheimer's. Unfortunately there have been no human trials proving effectiveness of cannabis in preventing the onset or delaying the progression of Alzheimer's, but research with animals has shown some promising results. The terpenoid pinene is desirable in these patients as it has been shown to enhance memory.[12]

Sources

[←1]

Eubanks, Lisa M., et al. "A molecular link between the active component of marijuana and Alzheimer's disease pathology." *Molecular pharmaceutics* 3.6 (2006): 773-777.

[←2]

Caoa, Chuanhai, et al. "The potential therapeutic effects of THC on Alzheimer's disease." *neurodegeneration* 24 (2014): 25.

[←3]

Benito, Cristina, et al. "The endocannabinoid system and Alzheimer's disease." *Molecular neurobiology* 36.1 (2007): 75-81.

[←4]

Aso, Ester, and Isidre Ferrer. "Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic." *Frontiers in pharmacology* 5 (2014).

[←5]

Eubanks, pp. 773-777.

[←6]

Iuvone, Teresa, et al. "Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on β-amyloid-induced toxicity in PC12 cells." Journal of neurochemistry 89.1 (2004): 134-141.

[←7]

Aso, Ester, et al. "Cannabis-Based Medicine Reduces Multiple Pathological Processes in AβPP/PS1 Mice." Journal of Alzheimer's disease: JAD 43.3 (2015): 977-991.

[←8]

Englund, Amir, et al. "Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-

dependent memory impairment." *Journal of Psychopharmacology* 27.1 (2013): 19-27.

[←9]

Fagherazzi, Elen V., et al. "Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders." Psychopharmacology 219.4 (2012): 1133-1140.

[←10]

Morgan, Celia JA, et al. "Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study." *The British Journal of Psychiatry* 197.4 (2010): 285-290.

[←11]

Englund, pp. 19-27.

[←11]

Russo, Ethan B. "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects." *British journal of pharmacology* 163.7 (2011): 1344-1364.

Anxiety and Depression

Cannabis has been used to treat anxiety and depression for thousands of years. A recent survey of patients seeking care in medical cannabis clinics in California reported that 38% (51% female, 33% male) of patients found relief from anxiety and 26% (35% female, 23% male) found relief from depression with cannabis use.[1]

Although research on the effectiveness of cannabis treatment of anxiety and depression in humans is limited, there is evidence of endocannabinoid system dysfunction in these patients.

- Women with major depression were found to have significantly decreased levels of the endocannabinoid 2-AG when compared to women without major depression, suggesting an endocannabinoid deficiency in these patients.[2]
- The same study found that levels of the endocannabinoid anandamide were low in women who had reported anxiety, again suggesting an endocannabinoid deficiency disorder.[3]
- A significant increase in Type I cannabinoid receptors was found in brains of individuals with a diagnosis of major depression who had committed suicide, compared to brain tissue of individuals who died of other causes, suggesting an endocannabinoid system abnormality in those that suffer with severe depression.[4]

The phytocannabinoids are well known to have anti-anxiety and antidepressant properties. THC, although very relaxing and mood enhancing for most people, can cause paranoia, anxiety and depressive episodes in some. Although there are many variables that can account for this paradox, three stand out.

- The first variable that can affect what type of response an individual patient may have depends on the potencies of THC and CBD in the cannabis product that is being used.
- The second variable is the dose and frequency of use, for instance, too much THC can give an undesired result.
- The third variable is the individual genetic factors that may affect a patient's anxiety response.

Many patients report less anxiety overall with intermittent use of low dose THC-rich cannabis. This approach can help the endocannabinoid system to run more smoothly and enhance endocannabinoid function. Large doses of

THC taken on a frequent basis can cause increased anxiety and panic attacks in some people – this may happen suddenly or over time. CBD has anti-anxiety properties in both low and moderate high doses.[5]

I have treated thousands of patients who suffer with anxiety and depression. Some patients prefer THC-rich cannabis, some prefer CBD-rich cannabis and some prefer a combination approach. Many have been able to stop using prescription medications and are using only cannabis to treat their condition. Others continue to use conventional treatment but they are able to keep the doses of these other medications low, which helps them to minimize the negative side effects well known to occur with these types of medications, such as sedation or dependence. Certain chemovars of cannabis may have more anti-anxiety effects, such as those that contain the terpenoid linalool, and others may have more anti-depressant effects, such as those containing limonene.

Patients sometimes report that they experienced anxiety and paranoia when they used cannabis recreationally when they were younger. Many of these patients are now finding good results with CBD-rich cannabis. I have also found that CBD can "antidote" THC-induced anxiety and paranoia if someone unintentionally takes too much THC.

Dosing is very important when using any cannabis containing THC. Starting at a low dose and titrating up slowly helps in minimizing any chance of unwanted side effects.

If you suffer with anxiety and/or panic, do not over medicate with THC-rich cannabis. Lower doses taken intermittently will work much better for you and will allow your endocannabinoid system to find balance. If you take large doses frequently, you will down-regulate (decrease) your cannabinoid receptors, which will result in loss of effectiveness of THC. My recommendation to my patients is to be very thoughtful about their use of THC-rich cannabis and to take breaks (from a few days up to a week) from cannabis when they are feeling well to minimize down-regulation of the receptors.

Sources

[←1]

Nunberg, H., et al. An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. *Journal of Drug Policy Analysis* (2011) 4

[←2]

Hill, Matthew N., et al. "Serum endocannabinoid content is altered in females with depressive disorders: a preliminary report." *Pharmacopsychiatry* 41.2 (2008): 48.

[←3]

Ibid.

[←4]

Hungund, B. L., et al. "Upregulation of CB1 receptors and agonist-stimulated [^{35}S]GTPS binding in the prefrontal cortex of depressed suicide victims." *Molecular psychiatry* 9.2 (2004): 184-190.

[←5]

Zuardi, A., et al. Action of cannabidiol on the anxiety and other effects produced by Δ 9-THC in normal subjects. Psychopharmacology (1982) 76: 245-50

Cindy's Story

A beautiful blonde woman in her mid-30's, Cindy has three children under the age of five years old and came to see me because she had been experiencing anxiety and difficulty sleeping since the birth of the second. The symptoms were getting worse and were starting to affect her relationship with her husband and children. She told me she was irritable and felt out of control, constantly nagging at her husband and children. Her primary care physician had recommended using a daily antidepressant and an "as needed" anti-anxiety pill, but after reading about the side effects of these medications, she was reluctant to take them.

Prior to meeting with me, Cindy had shared her struggles with a close friend who happens to be a medical cannabis patient herself. Her friend explained how cannabis was helping with her anxiety and she gave Cindy a CBD-rich edible to try. Cindy had experimented with cannabis a few times as a teenager and didn't care for the way it made her feel. Nervous about trying it again, she researched CBD on the internet and after learning of the lack of psychoactivity with CBD-rich cannabis, she decided to try it on a weekend when her husband was home to help with the kids just in case she didn't react well.

Cindy said the result was one of the best days she'd had in years. Relaxed and in control of her emotions, she was calm when dealing with the children and felt markedly happy. She chose not to tell her husband she had taken CBD, but he came up to her later in the day and told her that she seemed more like the easy-going girl he married. The positive results were so encouraging that Cindy's husband urged her to get medical cannabis approval from a physician.

When we first met, I educated Cindy on the endocannabinoid system, THC, CBD, and the various delivery methods for cannabis medicine. She found that a CBD-rich sublingual tincture used as needed for anxiety greatly improved her quality of life. Sleep also improved. She told me at a recent follow-up visit, "this treatment is so easy, just a few squirts of oil under the tongue and I'm more patient and loving to my children. I am in control of my emotions instead of being controlled by them. I'm happy again."

Cindy likely has an endocannabinoid dysfunction that causes a dysregulation of her neurotransmitters, which results in anxiety and insomnia. The pharmaceuticals her doctor prescribed work to regulate neurotransmitters, but they come with a long list of side effects that can create new problems. Reluctant to take synthetic medication on a daily basis, Cindy found that "as-needed" CBD-rich cannabis controlled her anxiety without any side effects. My medical opinion is that taking a non-toxic natural medication on an as-needed basis is preferable to taking a synthetic medication that requires daily

use and has possible side effects that include suicidality, weight gain, and insomnia.

I have seen thousands of patients like Cindy who function better with no toxicity from cannabis and who are living pharmaceutical free. I am aware that many people negatively judge Cindy and those like her who have chosen to use cannabis medicine instead of pharmaceuticals. I wonder if they would question the judgment of a young person standing in line at a pharmacy, waiting to pick up multiple prescriptions that can have terrible side effects. It is time we understand that we all have endocannabinoid systems, that there can be dysregulation in these systems that cause disease, and that these conditions can be effectively treated with cannabis medicine. The propaganda from the 1930's claiming that cannabis is "devil's weed" is no longer acceptable as the science of the endocannabinoid system is irrefutable. Cindy has found relief with no side effects from a plant. It's as simple as that.

Arthritis

There are over 350 million people worldwide that suffer with arthritis, the term for inflammation of joints. There are many different types of arthritis, including osteoarthritis, rheumatoid arthritis and psoriatic arthritis. The main symptoms of arthritis are joint pain and stiffness. Over time, there is degeneration and destruction of the joint. Numerous conventional medications are available for treatment of arthritis, but many patients report adverse side effects and minimal effectiveness.

Since cannabis works well for pain and inflammation with minimal side effects, many arthritis sufferers have chosen to use medical cannabis for treatment. In two surveys conducted in 2005, approximately 20-25% of patients suffering with arthritis reported symptom relief and improved quality of life with the use of medical cannabis.[1,2] Approximately 18% of patients presenting for a medical cannabis evaluation at a California clinic were seeking relief of arthritis symptoms.[3]

Numerous studies have investigated the effects of cannabis on inflammation and arthritis and are summarized here:

- Cannabis decreases inflammation by blocking the formation of the pro-inflammatory chemicals, called cytokines, that are made in the body in response to a trigger, such as an infection, injury, or a haywire immune system (autoimmune disease).[4,5,6]
- THC has been shown to have 20 times the anti-inflammatory potency of aspirin and two times the anti-inflammatory potency of hydrocortisone.[7]
- Cannabis extracts produced statistically significant improvements in pain on movement, pain at rest, quality of sleep and improved rating in a measure of disease activity for patients with rheumatoid arthritis.[8]
- In an animal study, the administration of CBD after the onset of collagen-induced arthritis effectively blocked progression of arthritis and had a potent anti-arthritic effect.[9]
- Daily administration of a synthetic cannabinoid was reported to protect joints from damage and to ameliorate collagen-induced arthritis in a murine model.[10]

Summarizing the available literature in the September 2005 issue of the *Journal of Neuroimmunology*, researchers at Tokyo's National Institute for Neuroscience concluded, "Cannabinoid therapy of rheumatoid arthritis could

provide symptomatic relief of joint pain and swelling as well as suppressing joint destruction and disease progression."[11]

Both THC and CBD have anti-inflammatory properties. Other phytocannabinoids such as cannabichromene (CBC) and tetrahydrocannabinolic acid (THCA) have anti-inflammatory properties as well. Arthritis patients report that medical cannabis use provides pain relief, reduces need for opiates and NSAIDS, improves mobility and promotes better sleep. Again what type of cannabis to use, THC-rich or CBD-rich or combination CBD+THC, and the delivery method is a personal preference depending on what works best for you. Since both THC and CBD are potent anti-inflammatories, most arthritis patients can customize their treatment to include daytime and nighttime use. There are a number of synergistic terpenoids that have anti-inflammatory properties as well, including β-caryophyllene, pinene and myrcene. Topical cannabis can be applied directly to an inflamed painful joint with fairly rapid onset relief.

Sources

[←1]

Swift, W., et al. Survey of Australians using cannabis for medical purposes. *Harm Reduction Journal* (2005) 4: 2-18

[←2]

Ware, M., et al. The medicinal use of cannabis in the UK: results of a nationwide survey. *International Journal of Clinical Practice* (2005) 59: 291-295

[←3]

Nunberg, H., et al. An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. *Journal of Dug Policy Analysis* (2011) Volume 4

[←4]

Malfait, A., et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proceedings of the National Academy of Science of the USA.* (2000) 97: 9561-9566

[←5]

Mechoulam, R., et al. Cannabidiol recent advances. *Chemistry & Biodiversity* (2007) 4: 1678–1692

[←6]

Carrier, E. Inhibition of an equilibrative nucleosidetransporter by cannabidiol: a mechanism of cannabinoidimmunosuppression. *Proceedings of the National Academy of Science of the USA.* (2006) 103: 7895–7900

[←7]

Evans FJ. Cannabinoids: The separation of central from peripheral effects on a structural basis. Planta Med. 1991;57:S60–7.

[←8]

Blake, D., et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* (2006) 45: 50-52

[←9]

Malfait, A., et al.

[←10]

Sumariwalla, P., et al. A novel synthetic, nonpsychoactive cannabinoid acid (HU-320) with anti-

inflammatory properties in murine collagen-induced arthritis. *Arthritis & Rheumatism* (2004) 50: 985-998

[←11]

Croxford, J., Cannabinoids and the immune system: potential for the treatment of inflammatory diseases. *Journal of Neuroimmunology* (2005) 166: 3-18

Asthma

It seems counterintuitive that cannabis would help people with asthma breathe more easily. In 1973, Dr. Donald Tashkin and his colleagues at UCLA published a study in the New England Journal of Medicine that showed that cannabis works as a bronchodilator, meaning it opens up the airways in both healthy and asthmatic people. He also found that cannabis "succeeded in reversing experimentally induced asthma, in a manner that was comparable to what could be achieved with a standard therapeutic bronchodilator that was widely used at the time."[1]

Other studies have reported improvement of asthma with cannabinoids:

- THC blocks a compound called acetylcholine, which works to maintain the muscle tone in the airways. This compound also causes tightening of the airways in an asthma attack. When THC binds to the cannabinoid receptor, it prevents the release of this compound and allows the airways to relax.[2]

Studies show that bronchodilation can be achieved with very small doses of THC.[3]

Smoking cannabis is not recommended especially for patients with asthma or other lung conditions. Heavy cannabis smoke is associated with increased risk for bronchitis and damage and inflammation of the lining of the airways has been reported in cannabis smokers.[4]

My patients with asthma who initially sought approval to use cannabis for other medical conditions have found, much to their surprise, that their co-existing asthma condition is improved and that they don't require as much asthma medicine.

I have a few patients in my practice who have significant symptoms of asthma that require them to take a number of daily medications that often cause adverse side effects. For some, despite intensive treatment with the latest asthma medications available, they report ongoing symptoms and occasional flare-ups that require hospital visits. By adding cannabis (not smoked), they report improved control of the asthma symptoms, less flare-ups, less hospitalizations and occasionally less need for asthma medications. In my experience, patients treating asthma with cannabis are using THC-rich cannabis, mostly in low doses with vaporizers, sublingual tinctures or edibles. Some patients find chemovars rich in the terpenoids pinene and limonene, which have bronchodilatory effects, to be quite helpful.

Sources

[←1]

Tashkin, Donald P., Bertrand J. Shapiro, and Ira M. Frank. "Acute pulmonary physiologic effects of smoked marijuana and oral Δ 9-tetrahydrocannabinol in healthy young men." *New England Journal of Medicine* 289.7 (1973): 336-341.

[←2]

Grassin-Delyle, S., et al. "Cannabinoids inhibit cholinergic contraction in human airways through prejunctional CB1 receptors." *British journal of pharmacology* 171.11 (2014): 2767-2777.

[←3]

Tashkin, Donald P., et al. "Effects of Smoked Marijuana in Experimentally Induced Asthma 1, 2." *American Review of Respiratory Disease* 112.3 (1975): 377-386.

[←4]

Tashkin, D. P. "Smoked marijuana as a cause of lung injury." *Monaldi Arch Chest Dis* 63.2 (2005): 93-100.

Autism Spectrum Disorder

It has been hypothesized that since the endocannabinoid system controls emotional and behavioral responses, as well as social interaction, a disruption in this system may be a contributing factor in the development of autism. A number of recent scientific reports have investigated this hypothesis.

- One study looking at the role of the endocannabinoid system in Fragile X syndrome (a syndrome that causes learning disabilities, cognitive impairment and features of autism spectrum disorders) found that the genetic defect causing this syndrome caused abnormal endocannabinoid metabolism and activity.[1]
- >Another study on Fragile X syndrome and endocannabinoid dysfunction found that pharmacological enhancement of endocannabinoid signaling normalizes this defect and corrects behavioral abnormalities in a mice model of Fragile X syndrome.[2]
- Recent research has found evidence to support that acetaminophen can trigger autism by activating cannabinoid receptors.[3]
- In a rat model of autism, subjects that had prenatal disruption of their endocannabinoid system had behavioral abnormalities associated with autism spectrum disorder.[4]
- A clinical study performed on children ages 3-9 years old demonstrated that Type 2 cannabinoid receptors on white blood cells of children with ASD were increased (thought to be compensating for low endocannabinoid levels) compared with matched healthy controls.[5]

A case study published from Austria in 2010 documented the use of dronabinol (synthetic THC) in a six-year-old boy diagnosed with autism. He received dronabinol therapy for six months with no change in other therapies or initiation of any other new treatments. An examiner and his parents rated his behaviors on a scale. He had significant decreased hyperactivity, lethargy and irritability. Stereotypic behavior and speech also improved. There were no reported adverse side effects. The dosing for this child was synthetic THC (no CBD), initially starting with 0.62mg one time per day in the morning and at the end of six months, he was taking 1.2mg in the morning, 0.62mg in the afternoon and 1.86mg at night for a total daily dose of 3.68mg to achieve the reported improvements.[6]

Most of the families that come to my office seeking cannabis treatment for

their loved one with autism have tried multiple medications and interventions without success. Some of these patients respond to CBD-rich cannabis, some to THC-rich cannabis, and some to combination CBD+THC; more recently, I have seen a number of autism patients have unexpected significant improvements with THCA. I recommend starting with low dose sublingual drops as accurate dosing and titration is easiest with this method in the pediatric population (although some children may swallow the liquid if they cannot cooperate with holding the liquid under the tongue). Accurately tested edible products may work well. However, it is important that the parent or caregiver start with very low doses as THC-rich edible products can cause uncomfortable psychoactivity if the dose is too high.

In children I recommend starting with CBD-rich or THCA-rich oil, and adding in THC as needed to obtain the desired effects. Many of these patients appear to have a high tolerance to the psychoactivity of THC. This may be due to an endocannabinoid deficiency/dysfunction or to less sensitivity in general, as children have immature cannabinoid receptors.

Since it is unclear which patient may have higher tolerance, I recommend caution in using THC and always recommend starting with low milligram doses and titrating up as needed. The same approach holds true for adults with autism. Chemovars high in myrcene and/or linalool, both of which have calming effects, can be very helpful for these patients.

Although many patients with autism achieve good results with cannabis treatment, it can be frustrating to find the right preparation that gives the desired results. I encourage patients and their caregivers to experiment with different doses, different CBD:THC ratios, different chemovars and different delivery methods as each person responds uniquely.

Sources

[←1]

Maccarrone, Mauro, et al. "Abnormal mGlu 5 receptor/endocannabinoid coupling in mice lacking FMRP and BC1 RNA." *Neuropsychopharmacology* 35.7 (2010): 1500-1509.

[←2]

Jung, Kwang-Mook, et al. "Uncoupling of the endocannabinoid signaling complex in a mouse model of fragile X syndrome." *Nature communications* 3 (2012): 1080.

[←3]

Schultz, Stephen T. "Can autism be triggered by acetaminophen activation of the endocannabinoid system?." *Acta neurobiologiae experimentalis* 70.2 (2009): 227-231.

[←4]

Kerr, D. M., et al. "Alterations in the endocannabinoid system in the rat valproic acid model of autism." *Behavioural brain research* 249 (2013): 124-132.

[←5]

Siniscalco, Dario, et al. "Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders." *Journal of autism and developmental disorders* 43.11 (2013): 2686-2695.

[←6]

Kurz, René, and Kurt Blaas. "Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child." *Cannabinoids* 5 (2010): 4-6

Cancer

Many cancer patients are using medical cannabis to combat the symptoms associated with their disease and the challenging treatment. These patients report a number of benefits, including rapid relief of the nausea and vomiting associated with chemotherapy, appetite stimulation, pain relief, better sleep and less anxiety and depression that often accompany the diagnosis and treatment of cancer.

Chemotherapy-Induced Nausea and Vomiting

The first report in the literature of the effective antiemetic benefits of cannabis appeared in the **New England Journal of Medicine** in 1975. Twenty cancer patients who did not respond to conventional antiemetics received either THC or a placebo two hours before chemotherapy. Patients reported that they had less nausea without any significant side effects.[1]

In the 1970s and 1980s, several states, including California, New York, New Mexico and Michigan, researched the use of cannabis to combat nausea and vomiting in cancer patients. The studies reported that cannabis was found to be an effective treatment and was equal to or better than the conventional medications available at the time.

In 1979, a study at the National Cancer Institute compared the antiemetic effects of oral and smoked THC with oral and smoked placebos. The findings reported that THC was very effective at reducing nausea and vomiting. Interestingly, the concentration of serum THC was measured, and when the concentration was low, 44% of patients suffered with nausea and vomiting; at moderate concentrations, only 21% had symptoms, and at high concentrations, only 6% had symptoms. Researchers reported that the effectiveness of THC depended on how much was absorbed into the bloodstream. They compared oral versus smoking delivery methods and were able to show that smoked THC was absorbed more reliably.[2]

In 1988, investigators found that out of 56 cancer patients who did not get relief from standard anti-vomiting medications, 78% were symptom-free after use of cannabis.[3]

In 1995, Israeli researchers found that delta-8-THC (a cousin compound of delta-9-THC with less psychoactive activity) was quite effective in preventing nausea and vomiting in a group of pediatric cancer patients with negligible side effects.[4]

Despite research that supports the efficacy of cannabis, its use has not been encouraged and it remains illegal in many states. In states with medical

cannabis laws, a significant number of cancer patients are turning to it for prevention and treatment of nausea and vomiting. Newer medications have emerged that are very effective for chemotherapy-induced nausea and vomiting; however, there are some patients who do not respond to them or who cannot tolerate or afford them. For these patients, medical cannabis is a reasonable and viable alternative.

Anorexia and Weight Loss

Many cancer patients report diminished appetite and significant weight loss associated with cancer and its treatment. Cachexia, weakness and wasting of the body, commonly results and is notoriously difficult to alleviate. The well-known side effect of the "munchies" – increased appetite – is often what drives cancer patients to seek out medical cannabis.

Over the past 20 years of research, investigators have shown that cannabis and the cannabinoid receptors have been shown to play an important role in the desire for food. A number of studies looking at the effects of cannabis and the cannabinoids on appetite and weight gain are summarized below:

- Men who smoked cannabis consumed 40% more calories than those that smoked a placebo,[5]
- Rats injected with anandamide (an endogenous cannabinoid) ate twice as much as rats given saline injections, but when the cannabinoid receptor was blocked, anandamide injections did not increase eating behavior.[6]
- Oral THC given to Alzheimer's patients increased their weight.[7]
- Cancer patients given dronabinol (synthetic cannabis) increased their weight.[8]
- THC-treated cancer patients were found to have improved and enhanced chemosensory perception and reported that food "tasted better"; pre-meal appetite and the proportion of protein calories increased when compared to the placebo.[9]
- Rats given low-THC cannabis extract had significantly increased food intake and reduced latency to feed versus the extract without THC. Since the former extract contained other non-THC cannabinoids, the researchers concluded that these cannabinoids exert a stimulatory effect on appetite.[10]

Cancer Pain

Opioids remain the keystone for the treatment of moderate to severe cancer pain; however, some patients experience inadequate pain relief and

unacceptable side effects are common.[11,12] Many patients report that cannabis is quite effective at relieving cancer pain by itself and also in combination with opiates.

Cancer patients often report that they suffer with neuropathy (nerve pain). Cannabis as a treatment for the pain of neuropathy has been studied in HIV and MS patients and has been found to be quite helpful in alleviating symptoms (see section on analgesia). The numbers of studies on the use of cannabis for cancer pain in human trials is limited; however, results clearly show that cannabis treatment is helpful without causing adverse side effects.

- Significant pain relief was obtained with higher doses of oral THC versus the placebo; pain relief peaked at three hours and was still near maximum six hours after the dose.[13]
- Another study compared two different doses of oral THC compared to two different doses of oral codeine. The higher doses of each medication was found to significantly reduce pain when compared to the placebo.[14]
- 39 patients who did not respond to chronic opiate treatment of pain received combination THC:CBD extract and reported decreased pain, improved sleep and less fatigue with no development of tolerance or loss of effect over time.[15]
- A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial study of a THC:CBD extract versus THC extract versus a placebo in relieving pain in patients with advanced cancer who were experiencing inadequate analgesia despite chronic opioid dosing, found that the pain relief from THC:CBD extract was statistically significant versus the placebo. The THC alone showed no significant improvement versus the placebo.[16]

In those cancer patients who are having difficulty controlling pain, cannabis is a viable option as it may be safely used alone or combined with opiates to give significant relief without adverse side effects.

I have evaluated hundreds of cancer patients using cannabis and many of them find enhanced appetite, better mood, pain relief, improved sleep and less fatigue. They report that cannabis has helped them tolerate chemotherapy and radiation and the difficult side effects they cause. Some patients reported that they didn't think that they would have continued with treatment if they didn't have cannabis available to provide desperately needed respite.

Cannabis as a Cure for Cancer

Cannabis as a cure for cancer is a controversial topic. Since cannabis is classified as a Schedule I controlled substance, research on the anticancer properties in human clinical trials has been prohibited. As of the writing of this book, there is one published human trial on cannabis use as an anticancer compound with a second trial in progress (both in Europe).

There exists, however, a significant body of scientific research that shows both THC and CBD have anti-cancer properties in certain cancers.

Both compounds have been shown to cause cancer cells to commit suicide (called apoptosis), inhibit tumor growth, inhibit metastasis and cancer cell migration, and inhibit angiogenesis, which is the growth of blood vessels that feed tumors.[17,18] Additionally, recent research has also shown that phyto-cannabinoids can work synergistically with certain chemotherapies to enhance the anticancer effects.

The following is a short list of recent research that documents the anticancer effects of cannabinoids. This is by no means a complete review of the scientific literature as there are thousands of articles that have been published in the last two decades exploring the potential of cannabis as an anticancer agent. It is important to note that these are not human trials.

- THC resulted in the activation of autophagy (cell self-digestion), loss of cell viability, and activation of apoptosis of melanoma cells.[19]
- Combining the chemotherapy drug gemcitabine with cannabinoids synergistically and strongly inhibited growth of human pancreatic tumor cells grafted in mice without apparent toxic effects.[20]
- CBD induced cell death of breast cancer cells through receptor independent mechanisms.[21]
- CBD significantly reduced primary tumor mass as well as the size and number of lung metastatic foci in two models of metastasis, and CBD inhibited human breast cancer cell proliferation and invasion.[22]
- Synthetic cannabinoids that bind to Type 1 and Type 2 cannabinoid receptors were given to mice with non-small cell lung cancer with the results of reduced proliferation and vascularization, and increased apoptosis of cancer cells.[23]
- THC was found to decrease cell proliferation and increase cell death of human glioblastoma multiforme cells.[24]
- THC induces apoptosis in colorectal cancer cells through the activation of the CB1 cannabinoid receptor.[25]

- THC is a potent inducer of apoptosis in three leukemic cell lines at low concentrations and as early as six hours after exposure.[26]
- CBD was found to increase the uptake of certain chemotherapeutic agents by malignant glioma cells, increasing the effectiveness of the chemotherapy.[27]

In the only published human trial, researchers in Spain directly administered THC into glioblastoma multiforme cancer cells in terminal patients and found that it inhibited tumor cell proliferation without any adverse side effects.[28]

Because cannabis remains federally illegal in the United States, research in humans is prohibited. However, in states that have legalized medical cannabis, many desperate cancer patients are using cannabis not only to treat symptoms, but also to treat the cancer directly. There are thousands of anecdotal reports of cancer patients using concentrated cannabis oils containing THC or CBD or both resulting in complete resolution of cancer. Cannabis for cancer treatment is not FDA approved nor is it considered standard of care by regulatory medical boards. However, patients who are not responding to standard cancer treatment are seeking it as an alternative therapy. The main concerns for these patients are dosage, whether to take CBD or THC or both, and the duration of treatment. All of these questions remain unanswered and continue to be a roadblock to those seeking life-saving cannabis therapy.

As a cannabis physician I have many patients use concentrated cannabis oil for cancer treatment, with or without conventional chemotherapy and/or radiation. Some of my patients have had incredible results with complete resolution of the cancer. A number of my patients with advanced cancers who were told that they only had a few months to live are living months or years beyond their prognosis. I believe that cannabis treatment can extend life and possibly cure cancer when given early in the course and in relatively high doses.

Although I am overjoyed when my patients improve, as a scientist I am quite frustrated by the lack of research. We must find the answers to these crucial questions so that patients who are suffering with aggressive and advanced cancers can have cannabis therapy as an option. If research on dosing, duration of treatment and cannabinoid profile to treat specific cancers can be performed, we will be able to use cannabis as a non-toxic chemotherapy and save lives.

Sources

[←1]

Sallan, S., et al. Antiemetic effects of delta-9-tetrahydocannabinol in patients receiving cancer chemotherapy. *New England Journal of Medicine* (1975) 293: 795-797

[←2]

Chang, A., et al. Delta-9-tetrahydrocannbinol as an Antiemetic in Cancer Patients Receiving High-dose Methotrexate: A Prospective, Randomized Evaluation. *Annals of Internal Medicine* (1979) 91: 819-824

[←3]

Vinciguerra, V., et al. Inhalation marihuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* (1988) 88: 525-527

[←4]

Abrahamov, A., et al. An efficient New Cannabinoid Antiemetic in Pediatric Oncology. *Life Sciences* (1995) 56: 2097-2102

[←5]

Foltin, R., et al. Effects of smoked marijuana on food intake and body weight of human living in a residential laboratory. *Appetite* (1988) 11: 1-14

[←6]

Williams, C., et al. Anandamide induces overeating: Mediation by central cannabinoid (CB1) receptors. *Psychopharmacology* (1999) 143: 315-317

[←7]

Volicer, L., Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* (1997) 12: 913-919

[←8]

Gorter, R., Management of anorexia-cachexia associated with cancer and HIV infection. *Oncology* (1991) 5:13-17

[←9]

Brisbois, T., et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Annals of Oncology (2011)

[←10]

Fairmond, J., et al. A low delta-9-tetrahydrocannabinol cannabis extract induces hyperphagis in rats. *Behavioural Pharmacology* (2010) 21: 769-772

[←11]

Scottish Intercollegiate Guidelines Network. Control of pain in patients with cancer: A National Clinical Guideline. Edinburgh, Scotland (2000) 44: 1-79

[←12]

Cleeland C., et al. Pain and its treatment in outpatients with metastatic cancer. *New England Journal of Medicine* (1994) 330: 592-596

[←13]

Noyes R., et al. The analgesic properties of delta-9-tetrahyrocannabinol. *Journal of Clinical Pharmacology* (1975) 15: 139 – 43

[←14]

Noyes R., et al. The analgesic properties of delta-9-THC and codeine. *Clinical Pharmacology and Therapeutics* (1975) 18: 84 – 9

[←15]

Johnson, J., et al. "An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics." Journal of pain and symptom management 46.2 (2013):207-218

[←16]

Johnson, J., et al. Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain. *Journal of Pain and Symptom Management* (2010) 39: 167-179.

[←17]

Velasco, Guillermo, et al. "The use of cannabinoids as anticancer agents." *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 64 (2016): 259-266.

[←18]

Ramer, Robert, and Burkhard Hinz. "Chapter Two-New Insights into Antimetastatic and Antiangiogenic Effects of Cannabinoids." *International review of cell and molecular biology* 314 (2015): 43-116.

[←19]

Armstrong, Jane L., et al. "Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death." *Journal of Investigative Dermatology* 135.6 (2015): 1629-1637.

[←20]

Donadelli, M., et al. "Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism." *Cell death & disease* 2.4 (2011): e152.

[←21]

Shrivastava, Ashutosh, et al. "Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy." *Molecular Cancer Therapeutics* 10.7 (2011): 1161-1172.

[←22]

McAllister, Sean D., et al. "Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis." *Breast cancer research and treatment* 129.1 (2011): 37-47.

[←23]

Preet, Anju, et al. "Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non–small cell lung cancer growth and metastasis." *Cancer Prevention Research* 4.1 (2011): 65-75.

[←24]

Mc Allister, Sean D., et al. "Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells." *Journal of neuro-oncology* 74.1 (2005): 31-40.

[←25]

Greenhough, Alexander, et al. "The cannabinoid δ9-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells." *International journal of cancer* 121.10 (2007): 2172-2180.

[←26]

Powles, Thomas, et al. "Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway." *Blood* 105.3 (2005): 1214-1221.

[←27]

Nabissi, Massimo, et al. "Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents." *Carcinogenesis* 34.1 (2013): 48-57.

[←28]

Guzman, M., et al. "A pilot clinical study of 9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme." *British journal of cancer* 95.2(2006):197-203.

Alexander's Story

Sixteen year old Alexander had been given only months to live when his parents brought him in to see me in April of 2015. I had come in on my day off, as my scheduler had notified me that this new patient had no time to wait for an appointment. In a wheelchair, cachectic and wearing a brace around his neck for support after surgery to remove a tumor in that area, Alexander had to be lifted by his father and placed on the examining table. He had no energy, seemed quite ill and very frail; and, while his parents said very little and appeared extremely nervous, they were eager to know if cannabis might help their son.

I learned that morning that Alexander had been diagnosed with Stage IV metastasized osteosarcoma (bone cancer) in early 2013 when he was thirteen years old. The path to diagnosis had been long and frustrating as Alexander had complained of leg pain for months, which his pediatrician had dismissed as "growing pains." When a lump appeared, he was finally sent to an oncologist who diagnosed him with the bone cancer that had already spread to his lungs. Chemotherapy was started and after a few months, he underwent surgery to remove the tumor in his leg.

In early 2014, all of his scans were negative for cancer cells, but a few months later, a lung tumor was discovered and he underwent another surgery. His mother shared with me that through all of this, Alexander remained "a trooper," and that while he had some down periods, he took everything that was happening to him in stride. "He's my hero," she said in a broken voice.

In January 2015, Alexander developed shoulder pain and an MRI revealed new tumors next to his spine. He underwent multiple surgeries to remove these tumors and started having postoperative fevers which did not resolve. One month later, another MRI revealed at least 30 metastatic lung tumors and another tumor next to the spine. At this point, Alexander had constant high fevers, wasn't eating and was vomiting all the time. He was taking multiple narcotics for the near-constant pain. By April of 2015, when he came to my office, his parents had been told to "put Alexander's affairs in order," that he could expect to live for a few more months.

His parents had heard about cannabis oil from a friend and they asked Alexander's oncologist about it. She was supportive and referred the family to me. I explained that cannabis would help their son with the nausea, vomiting, appetite and pain relief. I also explained that evidence in the scientific literature showed both THC and CBD killed cancer cells, stopped cancers growing and spreading and, that although human studies were lacking, I had some success treating cancer patients with high dose cannabis oil.

I recommended a regimen of concentrated CBD and THC oils, taken under

the tongue. We started the regimen with low doses and titrated up to high doses over a period of a few months. His mother later admitted to me that she thought there was no way that this tiny bit of oil could possibly help her son. Within three days, Alexander had perked up and within a week, the fevers went away and Alexander didn't need to take nearly as many pain pills. He also began eating and gained back some of the weight he had lost.

In July 2015, three months after starting the cannabis oil, Alexander had four scans to check on the cancer and to everyone's surprise, his scans showed no evidence of cancer. Another round of scans in November 2015 were also negative for cancer. Throughout his cannabis regimen, Alexander has continued to take chemotherapy in addition to the oils. He will continue to undergo scans every few months to make sure the cancer has not returned. As of the writing of this book, he remains cancer free.

Alexander's story seems quite incredible but there are a number of reasons why I believe his cancer has responded to cannabis treatment. Studies show that osteosarcoma cells die when treated with synthetic cannabinoids.[1],[2] Additionally two separate studies show that when cannabinoids are added to chemotherapies commonly used for osteosarcoma, specifically adriamycin and gemcitabine (both of which are quite toxic and only somewhat effective) the antiproliferative, antimetastatic, and antiangiogenic properties are enhanced, meaning that the cannabinoids and chemo work synergistically to fight cancer by stopping cancer growth, inhibiting the spread of cancer cells and blocking the cancer's ability to grow it's own blood vessels.[3],[4]

It's important to realize that these studies are conducted on cancer cells and animals in the laboratory. However, knowing that Alexander faced a certain death and knowing cannabis treatment is safe and non-toxic (certainly when compared to chemo), I felt he deserved a chance to try the oil. He has had extension of his life and it's possible that he will be cured of cancer with cannabis treatment.

Sources

[←1]

Hsu, Shu-Shong, et al. "Anandamide-induced Ca 2+ elevation leading to p38 MAPK phosphorylation and subsequent cell death via apoptosis in human osteosarcoma cells." *Toxicology* 231.1 (2007): 21-29.,

[←2]

Notaro, Antonietta, et al. "Involvement of PAR-4 in cannabinoid-dependent sensitization of osteosarcoma cells to TRAIL-induced apoptosis." *International journal of biological sciences* 10.5 (2014): 466.

[←3]

Niu, Feng, et al. "Potentiation of the antitumor activity of adriamycin against osteosarcoma by cannabinoid WIN-55,212-2." *Oncology letters* 10.4 (2015): 2415-2421.

[←4]

Donadelli, M., et al. "Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism." *Cell death & disease* 2.4 (2011): e152.

Diabetes

Diabetes is a group of metabolic and autoimmune diseases that result in high blood sugar. Type 1 diabetes mellitus, sometimes called juvenile diabetes or insulin-dependent diabetes, occurs when the pancreas is destroyed by the body's own immune system. The pancreas makes insulin, which is the hormone that converts sugar into energy and helps store sugar for future use. Type 2 diabetes mellitus occurs when insulin is produced but not used properly; this is also called insulin resistance. Patients with Type 1 diabetes require insulin to survive. Type 2 diabetes, which is currently being investigated as a possible autoimmune disease, can be controlled with dietary changes, oral medications, and sometimes insulin. High blood sugar from either type of diabetes can result in severe organ damage, including blindness, kidney damage, nerve damage and cardiovascular disease.

Type 1 Diabetes

Type 1 diabetes usually results from a genetic predisposition to immune dysfunction combined with an environmental trigger, most commonly a viral infection. Once triggered, the major components of the inflammatory system contribute to pancreatic cell destruction, specifically the cells that produce insulin. We have already learned that the cannabis plant contains numerous anti-inflammatory compounds. Researchers have sought to understand if cannabinoid compounds may prevent and/or delay progression of insulin-dependent diabetes. A number of studies have shown promising results:

- In an experimental model of mice with autoimmune diabetes (Type 1), THC caused a lowering of high blood sugar and decreased the loss of insulin by suppressing the severity of the autoimmune response.[1]
- In a study of non-obese diabetic mice (an experimental model for Type 1 diabetes), the development of diabetes was prevented when the mice were given CBD.[2]
- Mice with initial symptoms of diabetes who were given CBD had no progression of disease, had suppression of pro-inflammatory response and increased anti-inflammatory response.[3]
- CBD was found to significantly reduce heart muscle dysfunction, inflammation and cell death in a mouse model of Type 1 diabetes.[4]

Type 2 Diabetes

The endocannabinoid system is involved with energy metabolism, food intake and energy storage in animals and humans. It appears from research that cannabis users may be at lower risk of developing Type 2 diabetes:

- An inverse relationship between cannabis smoking and diabetes was found in a review of eight studies.[5]
- In a study sample of 579 cannabis users and 1,975 non-users, cannabis use was associated with lower levels of fasting insulin, lower insulin resistance and smaller waist size.[6]
- Cannabis users were found to have lower risk of diabetes than non-users in a study of 10,896 adults.[7]

It is important to understand that a dysregulation of the endocannabinoid system that often accompanies obesity (and may be caused by obesity), as explained in Chapter 3, may lead to the development of Type 2 diabetes. There is conflicting research as to whether THC is beneficial to Type 2 diabetics in the long run and further research is needed. However, there are numerous scientific reports that other phytocannabinoids found in cannabis may be beneficial to a person suffering with Type 2 diabetes and its complications:

- The phytocannabinoid THCV was shown to reduce glucose intolerance, improve glucose tolerance, increase sensitivity to insulin, and improve triglyceride levels.[8]
- CBD was found to protect diabetic animals from retinopathy (damage to the optic nerve) by reducing neurotoxicity and inflammation.[9,10]
- CBD prevented development of diabetic peripheral neuropathy in a mice model of diabetes.[11]
- CBD was found to lessen cell inflammation and cell damage and protect against diabetic complications such as atherosclerosis caused by high glucose levels.[12]

Of my patients with diabetes, the majority are Type 2 and only a few have Type 1. Most are using cannabis for other chronic medical conditions, including chronic pain, insomnia, anxiety and arthritis. These patients anecdotally report that they have better control of their sugar levels, that they exercise more, sleep better and overall have a sense of well being. For many people, cannabis use helps reduce stress and can promote better choices leading to a healthier lifestyle. I encourage all of my patients to include the use of CBD in their medication regimen, as its anti-inflammatory and antioxidant effects are very important for prevention of complications from diabetes.

Sources

[←1]

Li, Xinguang, Norbert E. Kaminski, and Lawrence J. Fischer. "Examination of the immunosuppressive effect of Δ 9-tetrahydrocannabinol in streptozotocin-induced autoimmune diabetes." *International immunopharmacology* 1.4 (2001): 699-712.

[←2]

Weiss, L., et al. "Cannabidiol lowers incidence of diabetes in non-obese diabetic mice." *Autoimmunity* 39.2 (2006): 143-151.

[←3]

Weiss, Lola, et al. "Cannabidiol arrests onset of autoimmune diabetes in NOD mice." *Neuropharmacology* 54.1 (2008): 244-249.

[←4]

Rajesh, Mohanraj, et al. "Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy." *Journal of the American College of Cardiology* 56.25 (2010): 2115-2125.

[←5]

Alshaarawy, Omayma, and James C. Anthony. "Cannabis Smoking and Diabetes Mellitus." *Epidemiology* 26.4 (2015): 597-600.

[←6]

Penner, Elizabeth A., Hannah Buettner, and Murray A. Mittleman. "The impact of marijuana use on glucose, insulin, and insulin resistance among US adults." *The American journal of medicine* 126.7 (2013): 583-589.

[←7]

Rajavashisth, Tripathi B., et al. "Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III." *BMJ open* 2.1 (2012): e000494.

[←8]

Wargent, E. T., et al. "The cannabinoid Δ9-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity." *Nutrition & diabetes* 3.5 (2013): e68.

[←9]

El-Remessy, Azza B., et al. "Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes." *The American journal of pathology* 168.1 (2006): 235-244.

[←10]

El-Remessy, A. B., et al. "Cannabidiol protects retinal neurons by preserving glutamine synthetase activity in diabetes." *Molecular vision* 16 (2010): 1487.

[←11]

Toth, Cory C., et al. "Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain." *Molecular pain* 6.1 (2010): 16.

[←12]

Rajesh, Mohanraj, et al. "Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption." *American Journal of Physiology-Heart and Circulatory Physiology* 293.1 (2007): H610-H619.

Epilepsy

Epilepsy is a broad term for a group of conditions characterized by seizures. There are over forty different types of epilepsy and many different types of seizures. The mainstay of treatment is antiepileptic drugs (AEDs). Other treatments include a restrictive diet (called the ketogenic diet), a vagal nerve stimulator (a pacemaker-like device implanted in the chest that sends a signal to disrupt the firing of nerves), and brain surgery to remove the area of the brain that may be causing the seizures.

Approximately 47-50% of patients with epilepsy will respond to the first AED that is prescribed. Of those that do not respond to the first AED, only 13% will respond to the second AED and less than 4% respond to the third AED. This means that despite numerous new antiepileptic medications hitting the market every year, approximately 33% of these patients still do not achieve seizure control.[1]

A seizure is defined as "clinical manifestation of a hyperexcitable neuronal network, in which the electrical balance underlying normal neuronal activity is pathologically altered – excitation predominates over inhibition."[2] The goal of AEDs is to stop seizures by enhancing inhibition or by opposing excitation of the neuronal activity. Unfortunately, for a significant portion of the population suffering with seizures, these medications may not be effective and may have severe adverse side effects.

As you have learned, the endocannabinoid system works by maintaining homeostasis. In simple terms, it balances cells by regulating the neurotransmitters, specifically sending messages to neurons to decrease excitation and promote inhibition. There is compelling scientific evidence to suggest that dysfunction of the endocannabinoid system plays a critical role in the development of seizures:

- In 2003, researchers reported that in a rat model of epilepsy, THC completely aborted seizures. When they blocked the Type 1 cannabinoid receptor, it resulted in increased seizure duration and frequency. They concluded that the ECS modulated seizure activity.[3]
- In another study, blocking Type 1 cannabinoid receptors in a laboratory epilepsy model resulted in status epilepticus (continuous long-lasting seizures).[4]
- Evaluation of surgically removed epileptic human brain tissue showed a 60% reduction of one of the enzymes required to make 2-AG (one of our endocannabinoids) and down-regulation of cannabinoid receptor mRNA. The authors concluded that the "neuroprotective machinery

involving endocannabinoids is impaired in the epileptic human hippocampus."[5]

- Cerebrospinal fluid levels of endocannabinoids were found to be reduced in patients with untreated newly diagnosed temporal lobe epilepsy.[6]

THC as antiepileptic

In a review of 31 animal studies investigating the antiepileptic effects of different doses of THC, THC showed an effective anticonvulsant effect in 61% of the subjects, had no effect in 29% of the subjects and was a proconvulsant (caused seizures) in 10% of the subjects.[7] Many adult patients with epilepsy report anecdotally that self-medicating with cannabis controls their seizures. I have numerous adult epilepsy patients in my medical practice that use low-dose THC-rich cannabis, either alone or in combination with an AED, who have excellent control of their seizure disorder and no reported adverse side effects. However, use of THC on a daily basis for seizure control can be quite difficult for patients who dislike the psychoactive properties. Development of tolerance to the effects may also be an issue with long-term chronic use of THC in this serious medical disorder.

Of note, in two separate instances, two of my adult patients who had never had seizures before reported to me that they experienced seizures after inadvertently overdosing on THC-rich cannabis edibles. Both patients, who were experienced cannabis users, ate an entire THC-rich candy bar that, unbeknownst to them, contained high amounts of THC (approximately 180mg). Each patient reported having a grand-mal seizure they had never experienced before or since. Both patients recovered quickly but were rightfully frightened by the experience. Although the amount of THC these patients ingested represents a THC overdose and is certainly not recommended dosing for most medical conditions, this shows that THC may have proconvulsant effects in humans at high doses.

CBD as antiepileptic

Scientific studies documenting the antiepileptic action of cannabis in humans are limited since we have not been free to research cannabis due to its Controlled Substance Schedule I designation. Importantly, CBD has been found to show anticonvulsant activity in all animal research. With the recent barrage of media attention on medical cannabis, specifically CBD use in pediatric epilepsy, researchers have focused on CBD-rich treatment as a viable option for patients with intractable epilepsy. Here is a review of the studies

that have looked at CBD treatment of epilepsy in humans:

- In 1978, nine patients with intractable epilepsy were randomized to treatment with CBD vs a placebo. Two of the four patients receiving CBD achieved seizure freedom and none of the five placebo patients reported improvement; no adverse side effects were reported.[8]
- In 1980, 16 patients with refractory seizures were randomized to receive CBD vs a placebo. Three of the CBD patients were seizure free, with four reporting improvement; of the placebo group, one reported improvement and seven reported no change.[9]
- In 1985, 12 adults with intractable seizures received either CBD or a placebo. No benefits were reported.[10]
- In 1990, 12 adults with intractable seizures received either CBD or a placebo. Some reduction of seizures with CBD were seen, but the results were not statistically significant and no side effects were reported.[11]
- In 2005, there was an open study of 18 pediatric patients with refractory epilepsy treated with CBD: "in most of the treated children an improvement of the crises was obtained equal to or higher than 25% in spite of the low CBD doses administered." There was clear improvement of consciousness and spasticity and no side effects were reported.[12]
- In 2013, Stanford researchers reported that, in a parent survey of 19 children with intractable epilepsy that used a CBD-rich whole plant extract, 11% became seizure free, 42% reported greater than 80% reduction in seizure frequency and 32% reported 25-60% seizure reduction, with the beneficial side effects of better sleep, improved alertness and better mood and the only adverse side effect was drowsiness.[13]
- In 2013, two Colorado neurologists presented a survey of 11 patients using CBD-rich oil where all patients reported reduction in seizures, with 73% reporting 98-100% reduction of seizures. At three months of treatment, 45% were seizure free and the oil was well tolerated by all patients.[14]
- In 2014 Epidiolex, a pure CBD extract made by GW Pharmaceuticals, started trials in the U.S. for children with severe refractory epilepsy. A total of 123 patients that received 12 weeks of continuous CBD therapy indicated an overall 46% decrease in seizure frequency from baseline, while patients with Dravet and Lennox-Gastaut syndromes showed a 51

and 52% decrease in seizure frequency, respectively.[15]

- In 2015, pediatric neurologists at UCLA Medical Center performed a survey of 117 parents of children with severe refractory epilepsy who were using CBD-rich oil. They reported that 85% of parents reported frequency of seizures were decreased and 14% reported seizure freedom. The only adverse side effect was increased appetite, but the beneficial side effects included improved sleep, mood and alertness.[16]

How does CBD reduce seizures

Recent research into the antiepileptic effects of CBD has revealed that it works at numerous sites in the brain to lessen the hyperexcitable state, thereby reducing seizures. CBD has been called a "promiscuous" molecule because of its multiple mechanisms of action.

CBD has been found to:

- Increase endocannabinoid levels by interfering with their breakdown (increased levels of endocannabinoids promote homeostasis in endocannabinoid deficiency states).
- Modulate the flow of ions (such as calcium and potassium) in neurons that reduces the excitability of the neuron.
- Suppress glutamate activity (glutamate causes neuronal excitation).
- Decrease neuroinflammation.

Inflammation of the brain, called "neuroinflammation", has been extensively researched over the last two decades, both as a cause and a result of recurrent seizure activity.[17] The presence of neuroinflammation predisposes the brain to have more seizures. Research suggests that seizure-related inflammation may contribute to cell death.[18] CBD is a well known potent anti-inflammatory that works to reduce inflammation that may promote or result from seizure activity. This added benefit of CBD may be why many epilepsy patients appear to have cognitive improvement in addition to an antiepileptic effect. Many CBD-rich chemovars of cannabis also contain the terpenoid beta-caryophyllene, which has potent anti-inflammatory properties and is synergistic with CBD in its anti-inflammatory effects.[19]

CBD as Neuroprotectant and Stimulator of New Brain Cell Growth

Studies have shown that CBD acts as a neuroprotective agent.[20,21] Neuroprotection refers to the preservation of nerve cells, either by mechanisms that prevent cell damage or slow the progression of damage or disease. The mechanism by which CBD protects the brain is not completely understood but thought to be due to its effect on maintaining homeostasis of the flow of calcium in brain cells.[22]

CBD also stimulates growth of new neurons, especially in the part of the brain called the hippocampus.[23,24] The hippocampus is responsible for memory, spacial navigation and emotional response. The hippocampus can be the focus of seizures and can also sustain severe damage from repeated seizures. More research is needed to learn the significance of CBD's effects on the hippocampus, but certainly it is promising that CBD protects brain cells and encourages the growth of new neurons.

CBD Interactions with AEDs

CBD is metabolized in the liver by the enzyme system called "cytochrome P450." Many AEDs are metabolized in this system as well and drug-drug interactions can take place if both CBD and certain AEDs are present in the body at the same time. In an Epidiolex study, medications that showed blood level variation, meaning the levels were either increased or decreased after CBD was added to the medication regimen, included clobazam, valproate, levetiracetam, felbamate, lamotrigine, zonisamide, diazepam, and a number of others.[25] In some cases the AED dose required adjustment so that toxicity could be avoided.

It is very important that patients who take antiepileptic medications are aware of the possible drug interactions with CBD. *Patients on AEDs should be medically supervised when adding cannabis to their medication regimen.*

I have evaluated many adult and pediatric patients who have suffered intractable epilepsy who are now experiencing excellent results with CBD-rich oil taken either sublingually, orally or via G-tube. Parents and patients report reduction of seizures, improved alertness, improved memory, better mood, better sleep, better appetite, improved motor skills, improved social interaction and less use of AEDs. Approximately 75% of my patients with intractable seizures who were surveyed in April 2015 after three months of CBD use reported a reduction of seizure frequency of 25% or greater, with 38% reporting greater than 50% reduction and 12% reporting seizure freedom (total of 112 patients, ages 1 year to 44 years, unpublished results 2015). Less than 5% of patients reported adverse side effects, which included diarrhea and sedation. Of the patients who achieved seizure freedom, five weaned off all AEDs without a recurrence of seizures. There were approximately 10% who

either did not respond or who had worsening seizures that returned to baseline after discontinuation of CBD treatment.

Most patients begin treatment with CBD-rich medication in higher ratios (somewhere between 20:1 and 30:1), starting at a low dose and increasing every few weeks depending on results. Following levels of AEDs is recommended. Some patients add THCA to their CBD regimen for its anti-inflammatory and anticonvulsant effects; some who have not responded to CBD have responded to THCA treatment. Other patients have added low-dose THC with a result of seizure reduction. Patients in my practice have had success with CBD-rich chemovars that include Charlotte's Web, AC/DC, Canna-Tsu, Harlequin and Cannatonic. Important anticonvulsant terpenoids include β-Carophyllene, linalool, pinene, and limonene.[26]

As mentioned previously, cannabis treatment is very individual and trial and error may be required to find what is effective. For patients with intractable seizures, CBD is proving to be an effective treatment, but because of drug interactions and the life-threatening nature of epilepsy, medical supervision is highly recommended if cannabis treatment is going to be used.

Sources

[←1]

Kwan, Patrick, and Martin J. Brodie. "Early identification of refractory epilepsy." *New England Journal of Medicine* 342.5 (2000): 314-319.

[←2]

Bromfield EB, Cavazos JE, Sirven JI, editors. An Introduction to Epilepsy [Internet]. West Hartford (CT): American Epilepsy Society; 2006. Chapter 3, Neuropharmacology of Antiepileptic Drugs.

[←3]

Wallace, Melisa J., et al. "The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy." *Journal of Pharmacology and Experimental Therapeutics* 307.1 (2003): 129-137.

[←4]

Deshpande, Laxmikant S., et al. "Cannabinoid CB1 receptor antagonists cause status epilepticus-like activity in the hippocampal neuronal culture model of acquired epilepsy." *Neuroscience letters* 411.1 (2007): 11-16.

[←5]

Ludányi, Anikó, et al. "Downregulation of the CB1 cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus." *The Journal of neuroscience* 28.12 (2008): 2976-2990.

[←6]

Romigi, Andrea, et al. "Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy." *Epilepsia* 51.5 (2010): 768-772.

[←7]

Russo, Ethan B. "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects." *British journal of pharmacology* 163.7 (2011): 1344-1364.

[←8]

Mechoulam, R., and E. A. Carlini. "Toward drugs derived from cannabis." *Naturwissenschaften* 65.4 (1978): 174-179.

[←9]

Cunha, Jomar M., et al. "Chronic administration of cannabidiol to healthy volunteers and epileptic patients." *Pharmacology* 21.3 (1980): 175-185.

[←10]

Ames, F. R., and S. Cridland. "Anticonvulsant effect of cannabidiol." *South African medical journal= Suid-Afrikaanse tydskrif vir geneeskunde* 69.1 (1986): 14-14.

[←11]

Trembly, B., and M. Sherman. "Double-blind clinical study of cannabidiol as a secondary anticonvulsant." *Marijuana'90 International Conference on Cannabis and Cannabinoids. Kolympari, Crete, July 8*. Vol. 11. 1990.

[←12]

Pelliccia, A., et al. "Treatment with CBD in Oily Solution of Drug-Resistant Paediatric Epilepsies." Presented at the 2005 Congress on Cannabis and the Cannabinoids, Leiden, The Netherlands: IACM.

[←13]

Porter, Brenda E., and Catherine Jacobson. "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy." *Epilepsy & Behavior* 29.3 (2013): 574-577.

[←14]

Gedde, M., and E. Maa. "Whole Cannabis Extract of High Concentration Cannabidiol May Calm Siezures in Highly Refractory Pediatric Epilepsies." In Press with the American Epilepsy Society, 67th Annual Meeting, December 2013.

[←15]

Blair RE, Deshpande LS, DeLorenzo RJ. Cannabinoids: is there a potential treatment role in epilepsy? Expert opinion on pharmacotherapy. 2015;16(13):1911-1914.

[←16]

Hussain, Shaun A., et al. "Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox–Gastaut syndrome." *Epilepsy & Behavior* (2015).

[←17]

Vezzani, Annamaria, et al. "The role of inflammation in epilepsy." *Nature Reviews Neurology* 7.1 (2011): 31-40.

[←18]

Vezzani, Annamaria, and Tallie Z. Baram. "New Roles for Interleukin-1 Beta in the Mechanisms of Epilepsy." *Epilepsy currents* 7.2 (2007): 45-50.

[←19]

Russo, Ethan B.

[←20]

Drysdale, Alison J., et al. "Cannabidiol-induced intracellular Ca 2+ elevations in hippocampal cells." *Neuropharmacology* 50.5 (2006): 621-631.

[←21]

Mechoulam, R., and E. Shohami. "Endocannabinoids and traumatic brain injury." *Molecular neurobiology* 36.1 (2007): 68-74.

[←22]

Ryan, Duncan, et al. "Cannabidiol targets mitochondria to regulate intracellular Ca2+ levels." *The Journal of Neuroscience* 29.7 (2009): 2053-2063.

[←23]

Esposito, Giuseppe, et al. "Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPAR involvement." (2011): e28668.

[←24]

Campos, Alline C., et al. "The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system." *International Journal of Neuropsychopharmacology* 16.6 (2013): 1407-1419.

[←25]

Friedman, D., M. R. Cilio, and N. Tilton. "The effect of Epidiolex (Cannabidiol) on serum levels of concomminant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program." *American Epilepsy Society, Seattle, WA* (2014).

[←26]

Nóbrega de Almeida, Reinaldo, et al. "Essential oils and their constituents: anticonvulsant activity." *Molecules* 16.3 (2011): 2726-2742.

Mallory's Story

Two years ago, Tom, a married physician and father of four, drove to work exhausted after a particularly difficult night caring for Mallory, his 12 year old daughter, who suffers with a seizure disorder. She had been treated with over a dozen anti-seizure medications, but none had been successful controlling them, and Tom and his wife felt hopeless. Tom is deeply religious and that morning found himself praying to God for an end to their ordeal. "It will be okay if You take her during a seizure," he said aloud in his car, "If she dies, her suffering will be over." Desperate, frustrated and completely broken down from years of her refractory seizures, he felt he just could not allow Mallory and his family to continue to live with the terrible quality of life that had become their normal.

About a month after Tom appealed to God, he and his wife saw the CNN documentary "Weed". Tom immediately did his own research, had Mallory approved to use medical cannabis by a California physician, purchased CBD-rich oil and began giving it to her. Within 36 hours of the first dose, he says "she woke up," becoming more alert, talking and interacting with her parents and siblings. Within the first few months, her seizures were reduced by 90%. She went back to school. The special diet she was on was discontinued and she was weaned off one of the two seizure medications. She was finally present and truly part of the family.

When I met with Mallory and her family, they shared with me that she had tried a dozen seizure medications over many years without any improvement. They had her evaluated to see if brain surgery would help, but she wasn't a candidate. The combination of ongoing seizures and side effects of medications had made her a zombie. She hadn't been to school in three years. She didn't interact with her siblings or parents. She existed without really living.

Tom is like any parent, willing to do anything to help his daughter live, but he admits that he feels uncomfortable breaking federal law by giving her cannabis, a Schedule I Controlled Substance. Initially he was reluctant to give Mallory the oil as there was no scientific evidence that it would work for her disorder, but after seeing her dramatic improvement, he now goes around the country sharing his family's experience and his point of view as a father, physician and advocate of medical cannabis. He testified in Washington, D.C. before a US Senate Drug Caucus Hearing about the ongoing barriers to cannabis research. He feels guilty that he allowed himself to ever think that it would be okay for Mallory to die. He feels bad that other parents have had similar thoughts and he continues to advocate that medical cannabis must be an option without political obstacles.

Mallory has been on CBD-rich oil for two years. She still has a few seizures each week, but they are shorter and less intense and she recovers quickly. Tom reports that Mallory recently got angry with him over something he said to her when he was driving her to school. He felt overjoyed that she was able to have and express this emotion as just a few short years ago, she lacked any affect and her interactions with others were dull or nonexistent. He and his family feel that they have been saved.

Fibromyalgia

Fibromyalgia is a chronic debilitating condition that includes symptoms of chronic diffuse pain, sleep disturbance, migraine headaches, fatigue, joint pain and irritable bowel-type symptoms. Patients may have all or just some of these symptoms. Myofascial Pain Syndrome (MPS) is considered a subtype of fibromyalgia. It appears that all patients with these conditions suffer a heightened perception of pain thought to be due to abnormal processing of pain signals in the central nervous system. The mainstay of treatment is medication, primarily pain relievers such as NSAIDs and opiates, pregabalin (antiepileptic), duloxetine (antidepressant), muscle relaxants and sleep aids.

As discussed in Chapter 2, an endocannabinoid deficiency/dysregulation has been hypothesized to be a possible cause of fibromyalgia symptoms. Studies have not completely elucidated this theory, but there is some evidence of abnormal endocannabinoid levels in patients with fibromyalgia.[1] Recent studies show that fibromyalgia patients have increased levels of glutamate, an excitatory neurotransmitter that can cause inflammation and damage when it accumulates.[2] Fibromyalgia patients have been found to have higher blood levels of proinflammatory compounds which indicates abnormal inflammation may play a role.[3]

Several studies have investigated the effectiveness of cannabinoid treatment in fibromyalgia patients.

- A small group of fibromyalgia patients who received daily doses of THC and no other pain medications reported a significant reduction in daily recorded pain.[4]
- The synthetic cannabinoid called nabilone improved symptoms in 40 patients with fibromyalgia in a randomized, double-blind, placebo-controlled trial.[5]
- A recent study from Spain reported that fibromyalgia patients who used cannabis had a statistically significant reduction in pain and stiffness, enhancement of relaxation, and improved sleep with an increased feeling of well being.[6]

I have evaluated hundreds of patients with fibromyalgia in my medical practice. Many are not finding relief with conventional medications or are having adverse side effects that make the medications intolerable. The majority are able to discontinue use of prescription medications, as cannabis is effective in treating pain, mood, insomnia and inflammation. Patients find success with

THC-rich cannabis, CBD-rich cannabis and/or CBD+THC cannabis products depending on individual preference and response. Many patients prefer CBD-rich cannabis during the day, as there is no psychoactivity, and THC at night to promote better sleep. I encourage patients who find relief with THC-rich cannabis to also include some CBD in their regimen for added anti-inflammatory effects. Different methods of cannabinoid delivery depend on a patient's personal preference. Vaporizing or sublingual oil will have a much quicker onset than edible cannabis products.

Cannabis varieties reported to be helpful in these patients are CBD-rich chemovars, such as AC/DC, Harlequin, and Cannatonic, as well as those that contain the following terpenoids: β-Caryophyllene (anti-inflammatory and analgesic), pinene (anti-inflammatory) and linalool (analgesic and relaxing).

Sources

[←1]

Kaufmann, Ines, et al. "Anandamide and neutrophil function in patients with fibromyalgia." *Psychoneuroendocrinology* 33.5 (2008): 676-685.

[←2]

Harris, Richard E., et al. "Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia." *Arthritis & Rheumatism* 58.3 (2008): 903-907.

[←3]

Wang, Haili, et al. "Circulating cytokine levels compared to pain in patients with fibromyalgia—a prospective longitudinal study over 6 months." *The Journal of rheumatology* 35.7 (2008): 1366-1370.

[←4]

Schley, M., et al. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon, reflex flare, and pain relief. *Current Medical Research and Opinion* (2006) 22: 1269-1276

[←5]

Skrabek, R., et al. Nabilone for the treatment of pain in fibromyalgia. *The Journal of Pain* (2008) 9: 164-173

[←6]

Fiz, J., et al. Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. *Public Library of Science One* (2011) 6: e18440

Vicki's Story

When I first met Vicki, I connected with her right away. Comfortable in her own skin, I knew that if it weren't for our professional relationship, we might have been friends. She was struggling when I met her, taking several medications and strapped financially as she had no decent health insurance to cover her pre-existing conditions after being laid off. Despite her serious medical conditions, she was very positive with a great attitude.

As a business development consultant and one of the few women in an industry dominated by men, Vicki had sought medical help 20 years earlier for intense pain in her right shoulder and neck as well as constant flu and cold symptoms. She was put on pain medication and eventually diagnosed with chronic fatigue syndrome and fibromyalgia. She tried a number of different medications but never felt well as the medications had many unwanted side effects. She couldn't drive on the pain medication, was "out of it" during the day and couldn't sleep at night. She struggled with the decision to continue taking the medications and suffer the side effects or not take the medications and suffer with symptoms of her conditions. She worried that she wouldn't be able to go on.

Vicki began reading about cannabis as a natural option to treat her pain and came to my office to learn more. She has found that THC-rich medicine taken in small doses (one to two puffs) smoked in a joint two or three times a day eases her pain and insomnia. It also alleviates the anxiety that is so often associated with these medical conditions. Vicki states that she's a responsible user and knows what affects her mind and body. She does not drive after she smokes and, while she reports sometimes feeling euphoria, she most often feels relaxed and is able to sleep.

Vicki's former life of pain prohibited her from really participating in activities with her friends and family. Before cannabis, if she didn't sleep or had too much pain, she would often stay at home to "ride it out," and then feel too exhausted to leave. Her friends and family were frustrated with her, insisting that she didn't take care of herself. "This is what fibromyalgia does. This is how chronic fatigue affects me," she'd insist. "I have to stay home and take care of myself." Today, if she feels pain or discomfort, she has a very effective and non-toxic way to treat it. With medical cannabis, she can actively participate in her life.

When I asked Vicki if I could share her story in this book, she replied, "Cannabis has helped me to live again. I can tolerate pain. I sleep now, for the first time, really, in my life. I think I wouldn't have been able to go on if I hadn't found cannabis. It has given me my life back."

Gastrointestinal Illness

Colitis is inflammation of the lining of the colon. There are many causes of colitis, including infection, inflammatory bowel disease, ischemic and microscopic. Symptoms can include abdominal pain, diarrhea with or without blood and sometimes fever. Conventional treatment includes anti-inflammatory drugs, including steroids, immunomodulators, which work by decreasing the overall immune response, and more recently available biologicals, which work by targeting a specific component of the immune system. These treatments can be quite effective but are often associated with significant adverse side effects and expense.

Evidence is building that suggests that the endocannabinoid system is involved in many processes in the gastrointestinal system, including inflammation, growth of cells that line the gut, motor function and pain perception.[1] Remember that the role of the endocannabinoid system is to maintain homeostasis of cellular function. The gastrointestinal system contains many cannabinoid receptors. Studies show that endocannabinoid dysfunction/deficiency may be the mechanism by which gut disease, especially inflammation, occurs.[2] Although much research is still needed, initial studies reveal lowered endocannabinoid levels in inflammatory bowel disease.[3]

Cannabinoids decrease intestinal motility (the movement of the bowel musculature that affects the transit of gut contents) in the normal gut.[4,5] Studies show that when the bowel is inflamed, as occurs in inflammatory bowel disease, activation of both CB1 and CB2 cannabinoid receptors helps to balance gut motility. What this means is that the diarrhea often associated with inflammatory bowel disease is reduced when these receptors are activated by cannabinoids. Quite interestingly, a lower dose of cannabinoids was effective in inflamed bowel when compared to healthy bowel, which is thought to be due to increased receptors being present in the disease state.[6,7] Researchers have also found that increasing the "healthy bacteria" in the gut increases the expression of Type 2 cannabinoid receptors, which modulate pain perception in the gut.[8]

I have evaluated thousands of patients with gastrointestinal disease who have had successful results with cannabis treatment. These patients report that many symptoms, including nausea, poor appetite, abdominal pain, diarrhea and bloating, respond to treatment with cannabis. Often patients with nausea and vomiting prefer to inhale as the onset of relief is immediate. Other patients have found success with sublingual tinctures and oils and especially with CBD-rich medicine due to its potent anti-inflammatory effects. Some

patients with gastrointestinal illness have reported an inability to use edible cannabis products as they can cause further gastrointestinal upset. As with other disease states, patients may find that THC-rich, CBD-rich or combination CBD+THC cannabis to be helpful depending on trial and error. I encourage patients with significant colitis symptoms to include CBD in their medicine regimen even if they find THC to be helpful. Terpenoids that have been found to specifically help the gut include terpinolene, beta-caryophyllene, limonene, and pinene.

Sources

[←1]

Izzo, Angelo A., et al. "Endocannabinoids and the Digestive Tract and Bladder in Health and Disease." *Endocannabinoids*. Springer International Publishing, 2015. 423-447.

[←2]

Di Sabatino, A., et al. "The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease." *Mucosal immunology* 4.5 (2011): 574-583.

[←3]

Marquéz, Lucia, et al. "Ulcerative colitis induces changes on the expression of the endocannabinoid system in the human colonic tissue." *PLoS One* 4.9 (2009): e6893.

[←4]

Aviello, G., B. Romano, and A. A. Izzo. "Cannabinoids and gastrointestinal motility: animal and human studies." *Eur Rev Med Pharmacol Sci* 12.Suppl 1 (2008): 81-93.

[←5]

Izzo, Angelo A., et al. "Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation." *British journal of pharmacology* 134.3 (2001): 563-570.

[←6]

Ibid.

[←7]

Izzo, Angelo A., et al. "Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil." *British journal of pharmacology* 129.8 (2000): 1627-1632.

[←8]

Rousseaux, Christel, et al. "Lactobacillus acidophilus modulates intestinal pain and induces

opioid and cannabinoid receptors." *Nature medicine* 13.1 (2007): 35-37.

Glaucoma

Glaucoma is a group of eye disorders that can damage the optic nerve. Most cases of glaucoma result from increased pressure in the eye, called ocular hypertension. If untreated or not properly controlled, this intraocular pressure increase can result in peripheral vision loss and eventually blindness.

The mainstay of glaucoma treatment is medication in the form of eye drops, laser surgery and conventional surgery. For many people these treatments are successful, however, there are some patients who are treatment resistant.

Multiple studies show that THC lowers intraocular pressure via the Type 1 cannabinoid receptor.[1],[2],[3],[4] In one particular study, 5mg of THC was found to transiently lower intraocular pressure, with effects lasting only four hours, while CBD and a placebo did not lower the pressure.[5]

In 2002, the Research Advisory Panel of California instituted the Cannabis Therapeutic Research Program to permit cannabis use on a compassionate basis while data was collected for research. Nine patients with glaucoma were enrolled to evaluate the effectiveness of THC on eye pressure. No conclusive results were obtained, except that after an initial lowering of eye pressure in four of the nine patients, the decreases were not sustained and all patients elected to stop treatment. The authors concluded that, "development of tolerance and significant systemic toxicity appears to limit the usefulness of this potential treatment."

I do not advocate the use of THC-rich cannabis as single drug therapy for glaucoma unless all other treatments have failed. I have a number of patients in my practice who find that the addition of THC-rich cannabis to their current glaucoma treatment has been beneficial, but I encourage these patients to stay on their vision-saving medications or to talk with their ophthalmologists about surgery if medications fail.

There are a number of mechanisms by which the optic nerve is damaged in glaucoma, including glutamate toxicity (glutamate is a neurotransmitter that is toxic when it accumulates) and inflammation. Both THC and CBD are well known neuroprotectants and have been shown to protect the optic nerve in experimental models of optic nerve crush injury,[6] glaucoma[7] and immune-mediated toxicity.[8] Based on these promising findings, I encourage my patients with glaucoma to include CBD-rich cannabis in their regimen to help prevent optic nerve damage.

Sources

[←1]

Hepler, Robert S., and Ira R. Frank. "Marihuana smoking and intraocular pressure." *Jama* 217.10 (1971): 1392-1392.

[←2]

Lockhart, Albert B., Manley E. West, and Henry IC Lowe. "The potential use of Cannabis sativa in ophthalmology." *West Indian med. j* 26.2 (1977): 66-70.

[←3]

Merritt, John C., et al. "Effect of marihuana on intraocular and blood pressure in glaucoma." *Ophthalmology* 87.3 (1980): 222-228.

[←4]

Porcella, Anna, et al. "The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies." *European Journal of Neuroscience* 13.2 (2001): 409-412.

[←5]

Tomida, Ileana, et al. "Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study." *Journal of glaucoma* 15.5 (2006): 349-353.

[←6]

Yoles, E, et al. "HU-211, a nonpsychotropic cannabinoid, produces short-and long-term neuroprotection after optic nerve axotomy." *Journal of neurotrauma* 13.1 (1996): 49-57.

[←7]

El-Remessy, Azza B., et al. "Neuroprotective effect of (−) Δ 9-tetrahydrocannabinol and cannabidiol in N-methyl-d-aspartate-induced retinal neurotoxicity: involvement of peroxynitrite." *The American journal of pathology* 163.5 (2003): 1997-2008.

[←8]

Mecha, Miriam, et al. "Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress." *Cell death & disease* 3.6 (2012): e331.

Hepatitis C and Liver Disease

The term "hepatitis" refers to inflammation of the liver. Hepatitis C specifically refers to an infection with the hepatitis C virus (HCV), a contagious infection that may either be a mild illness, lasting a few weeks, or serious, causing lifelong illness that attacks the liver. HCV is spread primarily through contact with the blood of an infected person and can be acute or chronic. Symptoms include nausea, vomiting, abdominal pain, weight loss, fatigue, joint pain and poor appetite. Approximately 75%–85% of people who become infected with hepatitis C virus develop chronic infection. Chronic hepatitis C can progress to cirrhosis (severe scarring of the liver) or liver cancer. An estimated 3.5 million people in the United States have chronic hepatitis C virus infection.

Conventional treatment of chronic hepatitis C consists of antiviral medications. Over recent years, new antiviral medications have become available with 80-100% cure rates depending on the strain of virus being treated. These medications are reported to have fewer side effects than their predecessors, although fatigue, depression, gastrointestinal upset, insomnia and joint pain may occur.

There are a number of scientific reports on the use of cannabis in patients with hepatitis C:

- Three studies found that patients with hepatitis C who used THC-rich cannabis daily (versus non-daily use) were at significantly higher risk of moderate to severe liver fibrosis.[1,2,3]
- A more recent study from 2013 reported no link between cannabis use and progression of liver fibrosis in hepatitis C patients who were also HIV positive. The authors of this study reported that previous cross-sectional studies reporting an association between marijuana smoking and liver fibrosis may be biased by reverse causation as patients use more marijuana to relieve symptoms as liver disease progresses.[4]
- Hepatitis C patients who used cannabis who were on anti-viral medication to treat the disease were more likely to stay on treatment than patients who didn't use cannabis.[5]
- In a mouse model of hepatic encephalopathy (defined as a decline in brain function due to severe liver disease), CBD improved cognition and locomotion due to its anti-inflammatory effects and activation of the 5-HT_{1A} receptor.[6]

- CBD restored liver function and improved cognition and neurological function in mice with liver failure and hepatic encephalopathy.[7]
- CBD significantly reduced liver inflammation in a mouse model of ischemia-reperfusion, the cutting off blood flow then restoring it as is often seen in liver surgery or liver transplantation.[8]
- CBD protected mouse liver from acute alcohol-induced steatosis (the infiltration of liver cells with fat).[9]

Patients with hepatitis C infection may be reluctant to take conventional medications for other medical conditions, as they are concerned about further damage to the liver. For instance, patients with hepatitis who also have chronic pain conditions are often warned to avoid medications that contain acetaminophen (the active ingredient in Tylenol which is also combined with an opiate such as hydrocodone) because acetaminophen is a leading cause of acute liver failure, even at doses that are within the recommended range. Cannabis, especially CBD-rich chemovars, allows these patients to treat their pain without further liver damage.

I recommend that patients with liver disease who want to use cannabis treatment to use CBD-rich cannabis, and to include beta-caryophyllene,[10] as both have proven anti-inflammatory and liver protective effects. Limiting THC-rich cannabis to intermittent and low doses is the best approach in these patients.

Sources

[←1]

Hézode, Christophe, et al. "Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C." *Hepatology* 42.1 (2005): 63-71.

[←2]

Hézode, Christophe, et al. "Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C." *Gastroenterology* 134.2 (2008): 432-439.

[←3]

Ishida, Julie H., et al. "Influence of cannabis use on severity of hepatitis C disease." *Clinical gastroenterology and hepatology* 6.1 (2008): 69-75.

[←4]

Brunet, Laurence, et al. "Marijuana Smoking Does Not Accelerate Progression of Liver Disease in HIV–Hepatitis C Coinfection: A Longitudinal Cohort Analysis." *Clinical infectious diseases*

57.5 (2013): 663-670.

[←5]

Sylvestre, Diana L., Barry J. Clements, and Yvonne Malibu. "Cannabis use improves retention and virological outcomes in patients treated for hepatitis C." *European journal of gastroenterology & hepatology* 18.10 (2006): 1057-1063.

[←6]

Magen, I., et al. "Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT1A receptor activation." *British journal of pharmacology* 159.4 (2010): 950-957.

[←7]

Avraham, Y., et al. "Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice." *British journal of pharmacology* 162.7 (2011): 1650-1658.

[←8]

Mukhopadhyay, Partha, et al. "Cannabidiol protects against hepatic ischemia/reperfusion injury by attenuating inflammatory signaling and response, oxidative/nitrative stress, and cell death." *Free Radical Biology and Medicine* 50.10 (2011): 1368-1381.

[←9]

Yang, Lili, et al. "Cannabidiol protects liver from binge alcohol-induced steatosis by mechanisms including inhibition of oxidative stress and increase in autophagy." *Free Radical Biology and Medicine* 68 (2014): 260-267.

[←10]

Calleja MA, et al. The antioxidant effect of beta-caryophyllene protects rat liver from carbon tetrachloride-induced fibrosis by inhibiting hepatic stellate cell activation. Br J Nutr. (2013) 109(3):394.

Huntington's Disease

Huntington's disease (HD) is a progressive inherited neurodegenerative disorder that affects motor coordination, causing chorea (involuntary jerking movements). It also causes a mental and behavioral decline leading to dementia and severe disability. There is no cure for HD, but there are medications and interventions, such as physical therapy, that can help with the management of the symptoms.

Multiple experiments in animal models of HD have shown that the cannabinoids, specifically THC, CBD and CBG, exert a protective effect on the damaged nerve cells due to their neuroprotective, anti-inflammatory and neuroregenerative properties.[1,2,3,4] Cannabinoids have been examined in humans for relief of symptoms of chorea and behavior issues. The synthetic cannabinoid nabilone was found to improve symptoms in two studies[5,6] and worsen symptoms in another.[7] However, the use of a single synthetic cannabinoid in these studies means the "entourage effect" of whole plant cannabis is lost. There is anecdotal evidence that both THC-rich and CBD-rich chemovars help HD patients with less chorea, better sleep, better appetite and less behavioral issues. Despite it being an area of research that appears promising, there are no published studies to date that show that cannabis is effective in slowing down the disease progression of HD.

Patients with HD use cannabis to treat symptoms and to improve quality of life. Starting with low doses of cannabis, CBD-rich or combination CBD+THC, and adjusting the dose to achieve desired effect can help with symptom relief without causing uncomfortable psychoactivity. Some patients are taking CBD in high doses (200mg per day or more) with the hope that it will slow down the progression of HD.

Sources

[←1]

Fernández-Ruiz, J., et al.. "Endocannabinoids and Neurodegenerative Disorders: Parkinson's Disease, Huntington's Chorea, Alzheimer's Disease, and Others." *Endocannabinoids*. Springer International Publishing, 2015. 233-259.

[←2]

Fernández-Ruiz, J., et al. "Neurodegenerative disorders other than multiple sclerosis." *Handbook of cannabis, Oxford University Press, Oxford* (2014): 505-525.

[←3]

Sagredo, Onintza, et al. "Cannabinoids: novel medicines for the treatment of Huntington's disease." *Recent patents on CNS drug discovery* 7.1 (2012): 41-48.

[←4]

Sagredo, Onintza, et al. "Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease." *Journal of neuroscience research* 89.9 (2011): 1509-1518.

[←5]

Curtis A, Rickards H. Nabilone could treat chorea and irritability in Huntington's disease. *Neuropsychiatry Clin Neurosci* 2006; 18:553-4.

[←6]

Curtis A, Mitchell I, Patel S, Ives N, Rickards H. A pilot study using nabilone for symptomatic treatment in Huntington's disease. *Mov Disord* 2009; 24: 2254-9.

[←7]

Müller-Vahl KR, Schneider U, Emrich HM. Nabilone increases choreatic movements in Huntington's disease. Mov Disord 1999;14: 1038-40.

Inflammatory and Autoimmune Conditions

The roles of the endocannabinoid system, endocannabinoids and phytocannabinoids in immune function and inflammatory conditions are a popular area of research. Both Type 1 and Type 2 cannabinoid receptors have been found on immune cells, suggesting that the endocannabinoid system is involved in our immune function. Studies have shown that cannabinoids can paradoxically both inhibit and stimulate the immune system in order to maintain homeostasis and control of immune responses. Cells of the immune system secrete numerous compounds that create inflammation, which may be a normal response to a trigger such as an infection, or it may be an abnormal "over-response" of the body which leads to inflammatory disease.

Cannabinoids have a potent inhibitory effect on cells of the immune system. In multiple animal studies, cannabinoids inhibit severity of disease, delay onset of disease and decrease inflammation.[1,2] Cannabinoids as anti-inflammatory agents have been researched in numerous autoimmune diseases, including Type 1 diabetes, rheumatoid arthritis, allergic asthma, multiple sclerosis, colitis, chronic liver inflammation and cancers with inflammatory components.[3]

I have many patients who report excellent results using phytocannabinoids as anti-inflammatory medicine. Since medical conditions vary person-to-person and response to cannabinoid treatment varies as well, patients may respond to different cannabinoid profiles and doses. Some of my patients are only using THC-rich cannabis in low, intermittent doses with improvement of their inflammation as evidenced by their reports of less pain and better mobility. Other patients are using CBD-rich cannabis in a daily high-dose regimen to suppress inflammation that occurs in autoimmune disease. Some patients are using combination CBD+THC in various ratios depending on what works best for their symptoms. As mentioned earlier, CBD-rich cannabis should be included in any regimen aiming for potent anti-inflammatory effects.

Sources

[←1]

Croxford, J. Ludovic, and Takashi Yamamura. "Cannabinoids and the immune system: potential for the treatment of inflammatory diseases?." *Journal of neuroimmunology* 166.1 (2005): 3-18.

[←2]

Klein, Thomas W. "Cannabinoid-based drugs as anti-inflammatory therapeutics." *Nature Reviews*

Immunology 5.5 (2005): 400-411.

[←3]

Nagarkatti, Prakash, et al. "Cannabinoids as novel anti-inflammatory drugs." *Future medicinal chemistry* 1.7 (2009): 1333-1349.

Rebecca's Story

When Rebecca Tennison walked into my office one afternoon, I saw a very ill woman, completely closed in on herself, sad and lacking in any vitality. She looked like a wilted flower. She told me she felt like she was dying. I assured her that many patients with serious illness had improvements in well being after using cannabis medicine. Given she was wracked with pain, it hurt to do anything and her multiple surgeries and illnesses had left her body a wreck, Rebecca believed she had nothing to lose in trying cannabis.

Rebecca thought she was beginning a new life after an abusive marriage when she enrolled in college and began work on her Associate's degree in 2005. She was 31 years old, made the honor's list each quarter, was balancing a new marriage and children and felt her growing knowledge and comprehension were immaculate. Toward the end of receiving her degree, she noticed her memory wasn't as sharp as it had been and that she couldn't comprehend new information. At night, she couldn't sleep and within months had become a severe insomniac. She began having night terrors, seeing and hearing things that were not there. She was referred to a psychiatrist who diagnosed her with both depression and anxiety and gave her medication. When her symptoms worsened, she was misdiagnosed with schizophrenia and was considered a candidate for institutionalization.

Rebecca and her family struggled for nearly 10 years with her worsening symptoms and the side effects of medications, as well as continued misdiagnoses. She gained a considerable amount of weight, couldn't tolerate touch because of near-constant pain, was unable to walk and needed a breathing treatment several times a day. She was ultimately diagnosed with lupus, fibromyalgia, a rare degenerative bone disease and a malformation of her hypothalamus. Prescribed more medications with debilitating side effects that included incontinence, lethargy and worsening insomnia, Rebecca decided she'd had enough and would rather die.

By this time, Rebecca had begun to hear stories about cannabis. A Mormon, Rebecca had been raised with the belief that one shouldn't ingest impurities and cannabis was certainly frowned upon as a bad drug. After learning about CBD and THC and different ways to use cannabis as medicine during that first visit with me, she began medicating with a sublingual CBD spray in a CBD:THC ratio of 18:1, using it first thing in the morning before getting out of bed and then at lunchtime. At night, she uses a spray that contains CBD:THC ratio of 1:1 to help with sleep in addition to helping with the pain.

The effects were nothing short of miraculous for Rebecca. While physical activity is still limited, she can walk again comfortably. She has energy for activities with her children. She can clean a stove, wash dishes and participate

in game nights with her family. She was able to stop all pharmaceuticals. Most extraordinarily, she sleeps at night and her extreme mood swings have lessened. While her memory isn't 100%, she is now able to retain new information and has enrolled in a program to become licensed as a financial adviser in the insurance industry. Because her memory and comprehension have improved so dramatically, she is determined to pass the exam and get on with her life.

Recently, Rebecca came back to see me for a follow-up visit. She walked in, her head high, a big smile on her face, her whole appearance so changed that even her energy level was palpable. No longer wilted, she appeared to me like a flower reaching toward the sun. Rebecca believes herself to be a walking testimony to the power of cannabis treatment. When I asked her how she feels about the change in her life, she said, "I can walk, drive, talk and think. I'm alive. I'm still around to see my kids".

Migraine Headaches

Migraine headaches are quite common, affecting 12% of the worldwide population. Migraine headaches usually start in response to a specific trigger. Typically there is mild pain that escalates to severe pain, characterized by throbbing or pulsing headache, often affecting one side of the head. Associated symptoms include nausea, vomiting and sensitivity to light and/or sound. Migraine sufferers may feel sensory warning symptoms, called an aura, prior to onset of the headaches. Migraines seem to run in families. The mainstay of treatment is a group of drugs called "triptans" which work by blocking the release of proinflammatory compounds in the brain. They are fairly effective for aborting or lessening severity of migraine headaches. Unfortunately, side effects can be significant and can include rebound headaches, pain or chest tightness, dizziness, nausea, vomiting, or warmth, redness, or tingling under the skin. Triptans are also costly and many insurance companies restrict the amount of these medications that can be dispensed to patients. Another group of medicines called ergot alkaloids are also prescribed for migraines, but they are less effective than triptans.

Unfortunately, little research exists that proves the mechanism by which cannabinoids alleviate migraines, despite the overwhelming anecdotal reports from patients suffering with them. Recent studies show that migraine headaches may be due to endocannabinoid deficiency and abnormal inflammatory response. Remember that the endocannabinoid system exists to maintain cellular homeostasis. Often migraine sufferers report that headaches begin in response to a trigger, such as bright light, hunger, hormones, or certain smells or foods. The trigger event causes an imbalance in the brain, which should then trigger the production of endocannabinoids to maintain homeostasis. If one is deficient in endocannabinoids, the imbalance continues, leading to development of the migraine headache. The trigger may also cause inflammation, which may become out of control and contribute to the resulting pain.

The few studies that have looked at the link between migraines and the ECS are summarized here:

- Endocannabinoids and synthetic cannabinoids inhibited receptors that control vomiting and pain, working to block these symptoms.[1]
- THC reduces serotonin release (which blocks vomiting and pain) from the platelets of human migraine sufferers.[2]
- Cannabinoids were found to bind to areas of the periaqueductal gray matter (an area of the brain that modulates pain transmission), which

have been implicated in migraine generation.[3]

- Three cases were reported of chronic heavy users of cannabis developing severe migraine attacks after abrupt cessation of use. The authors suggested that these rebound attacks are similar to the rebound headaches experienced by migraine patients when they abruptly stop other migraine treatment.[4]
- Genes that allow for increased inflammation were found in migraine patients and not found in control subjects.[5]
- Endocannabinoid levels were decreased in patients with chronic migraine and medication-over-use headaches suggesting that endocannabinoid dysfunction is involved in these two chronic conditions.[6]

Cannabis has been used for thousands of years to treat headaches. Medical cannabis patients are finding relief of pain, less nausea and better sleep. Patients also report less frequency and less severity of their migraine headaches with medical cannabis use. A number of well-known trigger factors for migraine headaches, specifically sleep deprivation and anxiety or stress, are alleviated with cannabis, thereby reducing the number of migraine attacks. Patients also report that they spend less on expensive migraine medications, have less missed days at school or at work and have overall improved quality of life.

There is no question that THC-rich cannabis can help abort or lessen the severity of a migraine, especially if taken at the onset of the pain. Some patients report that low-dose, regular use of THC-rich medicine significantly reduces the frequency and severity of the headaches. Other patients report that daily CBD-rich cannabis prevents migraine from occurring. Once the headache begins, a rapid delivery method such as inhalation or sublingual tincture is preferred by most. Specific chemovar choice results from trial and error for most patients.

Sources

[←1]

Burstein, R., et al. "EHMTI-0354. Abnormal expression of gene transcripts linked to inflammatory response in the periosteum of chronic migraine patients: implications to extracranial origin of headache." *The journal of headache and pain* 15.1 (2014): 1-1.

[←2]

Rossi, Cristiana, et al. "Endocannabinoids in platelets of chronic migraine patients and

medication-overuse headache patients: relation with serotonin levels." *European journal of clinical pharmacology* 64.1 (2008): 1-8.

[←3]

Lichtman, A., et al. Investigation of Brain Sites Mediating Cannabinoid-induce Antinociception inRats: Evidence SupportingPeriaquaductal Gray Involvement. *Journal of Pharmacology and Experminetal Therapeutics* (1996) 276:585-93

[←4]

El-Mallakh, R. Marijuana and Migraine. Headache (1987) 27:442-43

[←5]

Burstein, R., et al.

[←6]

Rossi, Cristiana, et al.

Nina's Story

Nina is a thin young woman with dark hair and eyes. Pleasant and personable, she came to see me with complaints that her constant migraines were interfering with both her personal and work life. A 40 year old vice-president for a commercial real estate company and the married mother of a toddler, she had suffered from debilitating migraines since she was 14 years old. The migraine episodes had a predictable pattern that began with a headache a week before the actual migraine and, despite attempts to keep them at bay with multiple over-the-counter and prescription drugs (both heart and seizure medications), Nina was having three or four episodes of migraine a month and what she described as a constant headache otherwise. Seizure medications allowed her to function partially, but she experienced side effects. And, while acupuncture provided some relief, it was only temporary, and Nina would eventually crash and go to bed.

Nina's friends used cannabis recreationally, but she had never tried it. She was very interested in using cannabis as medicine and came to see me for advice. The effects were almost immediate. Nina finds that THC-rich medicine combined with a higher myrcene content (which helps with sleep) give her the best results. She uses a vaporizer mostly at night as it takes effect quickly. After a short period of trial and error, she found that only a few puffs were needed to decrease pain and promote sleep. Before cannabis, if she had a headache, she felt as if she were running at 20% capacity. A full-blown migraine would send her to bed for two to three days. Since she began using cannabis, Nina hasn't used medication other than ibuprofen for three years and has had only three migraines in that time.

Living with headaches and constant pain had become a way of life for Nina and when she looks back on that life, she realizes how much time had been wasted and how unnecessary the pain was. The positive effects on her and her family have been profound. She doesn't miss work because of migraines or need to go through the bureaucracy of submitting the Family Medical Leave of Absence forms she had done so many times over the years. Nina isn't worried about what she can eat or the triggers for migraines anymore and feels more like a normal person. She's happier and her family interactions have improved. She doesn't have to cancel family events or gatherings and is an active participant in her child's care.

"I have no idea how I would have handled a screaming baby and a migraine!" she exclaimed to me. Nina doesn't feel "high" and reports that she views cannabis as medication to be respected and used responsibly. She has educated her family and friends about it as she doesn't want others to suffer needlessly as she had. "The cannabis takes care of everything," she says. "I

have a new life."

Nina is another example of someone who very likely is suffering with an endocannabinoid deficiency. When she uses THC-rich cannabis, it works at the cannabinoid receptor to balance the neurotransmitters in her brain, which are sending an abnormal message of pain and inflammation. By specifically targeting this system, her symptoms have virtually resolved. Very simply put, the migraine medications that she found to be useless did not treat the root cause of the migraines. Nina is not just treating the symptoms of pain and insomnia, she is maintaining balance of her endocannabinoid system, which is why the number of migraines has dramatically decreased since starting cannabis treatment.

Multiple Sclerosis

Multiple Sclerosis (MS) is the most common autoimmune inflammatory disease, affecting 1 of every 1,000 persons worldwide. The immune system attacks the myelin protective covering of neurons in the brain and spinal cord, thus interfering with the ability of nerves to function properly. Symptoms include numbness and/or weakness of limbs, vision problems, body tingling or pain, fatigue, tremor, unsteady gait, bowel or bladder problems and muscle spasticity. Symptoms can progress over time or can come as episodes called attacks or flare-ups. There is no known cure for MS. Treatment is aimed at preventing attacks and at treating symptoms to maintain quality of life. Patients struggle with compliance with MS medications as they have many adverse side effects.

Numerous studies have examined the use of cannabinoids to treat MS. Much of the research comes from investigations on the efficacy of Sativex (GW Pharmaceuticals), a sublingual preparation of CBD and THC in a 1:1 ratio, which is the only cannabis-based medication currently approved in 27 countries (not the U.S.) for treatment of MS spasticity. Sativex has been shown to be effective for spasticity, intractable peripheral neuropathy and MS-induced pain.

Here is a summary of some of the research of cannabis use for MS:

- In 1981, neurologists evaluated nine patients with MS who reported significant spasticity before and after using inhaled cannabis. In the double-blinded study, the blinded examiner evaluated muscle tone, reflexes, strength and EMG results both pre-and post-treatment with THC and was able to correctly identify which patients received THC in 78% of cases.[1]
- In 2001, an open-label pilot study of cannabis-based medicinal extract showed improved lower urinary tract dysfunction in 10 out of 10 patients with advanced MS refractory urinary tract dysfunction over eight weeks of treatment.[2]
- In 2003, investigators found cannabis to have statistically significant benefits versus a placebo for MS patients with urge incontinence.[3]
- In 2006, an extended open-label study of 167 MS patients found that whole plant cannabinoid extracts relieved pain, spasticity and bladder incontinence for a mean of 434 days without an increase in dose.[4]
- In 2007, another extended two year, open-label extension trial reported

that whole plant cannabis extracts was associated with long-term reduction of pain in select MS patients, with fewer daily doses and lower median pain scores the longer they were on the medication.[5]

- In 2010, investigators at the University of California at San Diego reported that inhaled cannabis significantly reduced objective measures of pain intensity and spasticity in patients with MS in a placebo-controlled, randomized clinical trial. Investigators concluded that "smoked cannabis was superior to placebo in reducing spasticity and pain in patients with multiple sclerosis and provided some benefit beyond currently prescribed treatment."[6]
- In 2014, Spanish researchers treated 50 MS patients with inhaled CBD+THC for spasticity and pain, and found it to be 80% effective.[7]
- In 2015, in a mice model of MS, Sativex improved motor activity, reduced brain cell damage and CBD was found to alleviate motor deterioration.[8]

A survey in 2002 reported that almost 50% of MS patients use cannabis medically.[9] Another survey in 2006 reported that those with increased disability were more likely to use cannabis.[10]

I have seen many patients with MS that report that cannabis use reduces pain, lessens spasticity, alleviates depression, lessens fatigue and decreases incontinence. They report that cannabis acts as a potent and quick-acting muscle relaxant. As mentioned in previous chapters, cannabinoids serve a neuroprotective function and may inhibit the progression of disease, as well as boost immune function in MS patients. Most of my MS patients prefer using vaporizers or sublingual tinctures as these methods have quick onset and are easy to dose. Patients report using THC-rich, CBD-rich and combination CBD+THC cannabis based on their personal preference and response. Some experts recommend blending different chemovars as this enhances the cannabinoid content and terpenoid profile, which may improve effectiveness.

Sources

[←1]

Petro, D., et al. Treatment of Human Spasticity with Delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* (1981) 21: 413S-416S

[←2]

Brady, C., et al. Acute and Chronic Effects of Cannabis-Based Medicinal Extract on Refractory Lower Urinary Tract Dysfunction in Patients with Advanced Multiple Sclerosis: Early Results. *Congress of the IACM* abstracts (2001) 9

[←3]

Zajicek, J., et al. Cannabinoids for Treatment of Spasticity and Other Symptoms Related to Multiple Sclerosis: Multicentre Randomized Placebo-controlled Trial. *Lancet* (2003) 362: 1517-26

[←4]

Wade, D., et al. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms of multiple sclerosis. *Multiple Sclerosis (2006)* 12: 639-645

[←5]

Rog, D., et al. Oromucosal delta-9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clinical Therapeutics (2007)* 29: 2068-2079

[←6]

Corey-Bloom, J. Short-term effects of cannabis therapy on spasticity in multiple sclerosis. In: University of San Diego Health Sciences, Center for Medicinal Cannabis Research. *Report to the Legislature and Governor of the State of California presenting findings pursuant to SB847 which created the CMCR and provided state funding,* 2010

[←7]

Fernández, L. Lorente, et al. "Clinical experiences with cannabinoids in spasticity management in multiple sclerosis." *Neurología (English Edition)* 29.5 (2014): 257-260.

[←8]

Feliú, A., et al. "A Sativex®-like combination of phytocannabinoids as a disease-modifying therapy in a viral model of multiple sclerosis." *British journal of pharmacology* (2015).

[←9]

Reuters News Wire. August 19, 2002. "Marijuana helps MS patients alleviate pain, spasms."

[←10]

Chong, M., et al. Cannabis use in patients with multiple sclerosis. *Multiple Sclerosis* (2002) 12: 646-651

Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disorder that primarily affects motor function and coordination. PD results from the death of dopamine-producing nerve cells in the area of the brain in the basal ganglia called the **substantia nigra**, an area responsible for movement. The cause of PD in most cases is unknown. However, a small percentage of cases are genetic. There are some environmental risk factors that have been associated with increased risk of PD, including pesticide exposure and head injury. PD patients suffer with tremor, rigidity, slowness of movement and postural instability. Patients can also have depression, cognitive decline, sleep disorders and occasionally psychosis. The mainstay of treatment is medications, rehabilitation with exercise and occupational therapy and, in advanced cases, surgery may be recommended.

There is limited scientific literature on the effectiveness of medical cannabis for treatment of PD symptoms. One study reported no improvement in tremors with smoked cannabis.[1] In a survey of 339 patients with PD in the Czech Republic, 25% reported experimenting with cannabis to treat symptoms. Almost half of those using cannabis reported improvement with at least once-a-day use. Use over three months resulted in more significant alleviation of symptoms. Only four patients reported worsening symptoms with cannabis use. The researchers reported that "long-term regular use of cannabinoids is crucial" to obtaining good results with cannabis for PD.[2]

In 2014, Israeli researchers reported that 22 patients were evaluated for severity of symptoms at baseline and after smoked cannabis treatment. The patients reported significant improvement in tremors, rigidity and slowness of movement, with improvement of sleep and pain as well.[3]

In a recent survey of PD patients using alternative treatments in Colorado, nine patients (out of 207) reported using cannabis resulting in improved sleep and mood. Two of the nine patients reported improved motor symptoms and quality of life.[4]

A small study of six patients with psychosis of PD (which may have been related to medication) who were given high dose CBD for four weeks, showed that all patients had significant improvement of thinking, less withdrawal, better sleep, fewer hallucinations and some improvement in motor function.[5]

Interestingly, the endocannabinoid system goes through various changes during the progression of PD, in part as a response to the onset of disease, and then as a result of the disease. It appears that certain cannabinoids may help early in the disease process and then may aggravate the condition as it

progresses.[6]

There is experimental evidence that CBD is effective at delaying the progression of PD due to its neuroprotective, anti-inflammatory and antioxidant properties. Another phytocannabinoid, THCV, has been investigated for use in PD in combination with CBD as it has anti-inflammatory properties with little to no psychoactivity at low doses.[7,8]

A number of my patients with PD have reported the benefits of using different methods of delivery and different cannabinoid profiles. Some patients have found relief of tremors with inhaled THC and others have not. A few patients have found relief with high doses of CBD-rich cannabis taken sublingually. Some patients are using combination CBD+THC.

As mentioned, trial and error is needed to find what cannabinoid profile and method will work best. Starting low-dose and titrating up is recommended, particularly with THC-rich cannabis. Unfortunately, THCV-rich varieties are not readily available.

Sources

[←1]

Frankel, J. P., et al. "Marijuana for parkinsonian tremor." *Journal of neurology, neurosurgery, and psychiatry* 53.5 (1990): 436.

[←2]

Venderová, Kateřina, et al. "Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms." *Movement Disorders* 19.9 (2004): 1102-1106.

[←3]

Lotan, Itay, et al. "Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study." *Clinical neuropharmacology* 37.2 (2014): 41-44.

[←4]

Finseth, Taylor Andrew, et al. "Self-Reported Efficacy of Cannabis and Other Complementary Medicine Modalities by Parkinson's Disease Patients in Colorado." *Evidence-Based Complementary and Alternative Medicine* 2015 (2015).

[←5]

Zuardi, A. W., et al. "Cannabidiol for the treatment of psychosis in Parkinson's disease." *Journal of Psychopharmacology* (2008).

[←6]

Fernández-Ruiz, Javier. "The endocannabinoid system as a target for the treatment of motor dysfunction." *British journal of pharmacology* 156.7 (2009): 1029-1040.

[←7]

Lastres-Becker, Isabel, et al. "Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease." *Neurobiology of disease* 19.1 (2005): 96-107.

[←8]

Fernández-Ruiz, Javier, et al. "Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?." *British journal of clinical pharmacology* 75.2 (2013): 323-333.

Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD) is a condition that is brought on by experiencing or witnessing a terrifying event. Not everyone who goes through a traumatic ordeal develops PTSD. Symptoms of PTSD include flashbacks, nightmares, disturbed sleep and/or severe anxiety that interfere with normal functioning. Recent research reports that there may be a number of genetic causes that may predispose certain people to create fear memories and subsequent PTSD symptoms.[1]

The mainstay of treatment for PTSD is therapy and/or medications such as antidepressants, anti-anxiety medications and antipsychotics. These medications may cause significant side effects (especially when taking more than one) and have been shown to have limited effectiveness.[2,3] PTSD sufferers are desperate for effective nontoxic treatment and many have found that cannabis helps to quell the nightmares, allows for sleep and alleviates anxiety.

Understanding how cannabis may help patients with PTSD is a major focus of research as the number of military veterans with this medical condition has increased significantly over the past few decades.[4]

The discovery of the endocannabinoid system (ECS) and the mapping of cannabinoid receptors has revealed that cannabinoid receptors are expressed in high levels in the part of the brain called the amygdala that controls anxiety, fear memory and emotional response to stress.[5] When these receptors are triggered by natural endocannabinoids or by THC, there is a reduction of anxiety and lessening of PTSD symptoms. In order to have a normal response to fear and to the resulting traumatic memories, a properly functioning ECS must be present. An abnormality in the ECS can predispose the individual to PTSD and the chronic stress that results from PTSD can further impair the functioning of the ECS, worsening the condition.

Although published research on the use of cannabis for PTSD is limited, there are some studies that show a relationship between the endocannabinoid system, PTSD and cannabis use:

- Nabilone, a synthetic cannabinoid that binds to the cannabinoid receptor similarly to THC, was found to stop nightmares or significantly reduce nightmare in 72% of PTSD patients who did not respond to conventional treatment, with some reporting improved sleep, improved quality of sleep and reduction of daytime flashbacks.[6]
- Low levels of the endocannabinoid anandamide (i.e. endocannabinoid

deficiency) were found in individuals with PTSD.[7]

- PTSD patients who were approved to use medical cannabis as part of the New Mexico Medical Cannabis Program reported over 75% reduction in symptoms with cannabis use.[8]
- In Israel, 10 patients with chronic PTSD were given 5mg of THC by mouth twice a day with statistically significant improvement in global symptom severity, sleep quality, frequency of nightmares and PTSD hyperarousal symptoms. Three patients reported mild adverse side effects but did not discontinue use of the medication.[9]

It is very important to note that patients with PTSD are desperate to find a solution to their disruptive symptoms and poor quality of life. Cannabis medicine can be very useful to treat many of the symptoms of PTSD, but it is critical that PTSD patients understand the concept of receptor down-regulation with THC use. Remember that chronic heavy use of THC-cannabis can cause a decrease in receptor numbers that will lead to tolerance and eventually to a loss of effectiveness.

Patients with PTSD must be thoughtful about frequency and dosing of THC-rich cannabis so that tolerance can be minimized and effectiveness can be maximized.

I have found in my medical practice that patients using moderate doses of THC who take intermittent breaks from use (a few days up to a week after they have improved symptoms) report excellent resolution of PTSD symptoms.

Unfortunately, I have evaluated a few patients with PTSD who no longer benefit from the use of THC-rich cannabis as they are over-medicating with high potency concentrated formulations that have created a very high tolerance. A number of these patients were able to abstain from cannabis for a few weeks in order to up-regulate their receptors which resulted in positive effects when they started to use THC-rich cannabis again. Use of high CBD:THC (approximately 18:1 to 25:1) cannabis during the time of abstinence helped to minimize THC withdrawal symptoms in these patients.

I encourage my patients to include CBD in their cannabis medicine regimen as it can be quite helpful in reducing anxiety. PTSD patients using chemovars with high THCV potency anecdotally report that this phytocannabinoid also helps to decrease anxiety and can block panic attacks without causing sedation. However, chemovars with significant amounts of THCV are quite rare to find at this time. Terpenoids that may help with PTSD symptoms include myrcene for its sedating effects, linalool for its calming effects, and limonene for anti-anxiety effects. Chemovars high in pinene are discouraged as this terpenoid aids memory, which may give the opposite effect that PTSD sufferers are

seeking.

Sources

[←1]

Sandica, B. A., and B. Pop. "Risk Factors for PTSD." *J Trauma Treat S* 4 (2014): 2167-1222.

[←2]

Friedman MJ, Marmar CR, Baker DG, et al. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. J Clin Psychiatry 2007;68(5):711–720.

[←3]

Berger, William, et al. "Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review." *Progress in neuro-psychopharmacology and biological psychiatry* 33.2 (2009): 169-180.

[←4]

Trezza, Viviana, and Patrizia Campolongo. "The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD)." *Frontiers in behavioral neuroscience* 7 (2013).

[←5]

Katona, István, et al. "Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission." *The Journal of neuroscience* 21.23 (2001): 9506-9518.

[←6]

Fraser, George A. "The use of a synthetic cannabinoid in the management of Treatment-Resistant nightmares in posttraumatic stress disorder (PTSD)." *CNS neuroscience & therapeutics* 15.1 (2009): 84-88.

[←7]

Neumeister, Alexander, et al. "Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study." *Molecular psychiatry* 18.9 (2013): 1034-1040.

[←8]

Greer, George R., Charles S. Grob, and Adam L. Halberstadt. "PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program." *Journal of psychoactive drugs* 46.1 (2014): 73-77.

[←9]

Roitman, Pablo, et al. "Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic post-traumatic stress disorder." *Clinical drug investigation* 34.8 (2014): 587-591.

Jeffrey's Story

One of the last to be drafted to fight in Vietnam, Jeffrey served and got out in April of 1975 during the fall of Saigon. He went immediately from the war into law enforcement, a thrill-seeker who was cited for bravery numerous times and commended for his work. "You couldn't kill me with a bullet," he told me. "I ate stress for breakfast."

It was many years later, when Jeffrey was 39 years old, that he experienced his first panic attack that felt like he was having a heart attack. He found himself in the hospital facing a barrage of doctors who refused to acknowledge anything was wrong with him. Prescribed multiple drugs, including Wellbutrin, Zoloft, Xanax and Clonazepam, Jeffrey made two suicide attempts and was finally diagnosed with late-onset post-traumatic stress disorder.

Despite his growing stress, lack of sleep, panic attacks and fits of anger, rage and violence, Jeffrey found little relief in the medications and virtually no support from his employer or the physicians treating him. He lost his job, his insurance and thus his ability to pay for the pharmaceuticals, so he had to stop taking them abruptly and plunged into withdrawal that included violent episodes.

In a self-described "lost place," a person who loved him dearly gave him a bag of marijuana and told him to smoke it. Jeffrey had smoked quite a bit of cannabis in Vietnam but hadn't touched it in years. He began self-medicating that day and immediately felt relief. He was able to sleep without the nightmares that had plagued him for years, an improvement that radically changed his days as well.

While Jeffrey acknowledges that PTSD is never curable due to the parts of himself that he'll never get back, he asserts that cannabis has been the catalyst that has gotten him close to what he calls "98% managed." He manages the symptoms of PTSD every day by medicating with full flower and concentrated forms, both smoking and vaping it, as well as using edibles. In "getting a breath of relief," the symptoms of PTSD become contained, and his loved ones can breathe in relief as well.

Jeffrey asserts that cannabis has made his life normal again. He is no longer on any pharmaceuticals. He is passionate about advocating for other war veterans with PTSD, despite the Veterans' Administration and many doctors' disapproval. He disagrees with their assertion that cannabis is only for stoners and stresses that using cannabis has brought balance to him and other veterans that use it.

"We were injured," he states, "and we have to treat our injuries. We have to tend our wounds the best we can. The scars never heal – your essence, your soul and your being, but with cannabis I laugh, love, make love, hug, cheer, cry

and celebrate. I'm a human being again."

Schizophrenia

Schizophrenia is a chronic, severe, and debilitating brain disorder that affects about 1% of the population. Delusions, hallucinations, movement disorders and disorganized thinking are considered positive symptoms. Negative symptoms include flat affect, social withdrawal and lack of pleasure in everyday life. Cognitive symptoms are poor attention, poor executive functioning and decision-making, and poor memory.

Hyperactivity of dopamine and serotonin, two important neurotransmitters, plays a critical role in the cause of schizophrenia. However, other neurotransmitters and their receptors are involved as well.[1] Cannabinoid receptors exist in high numbers in the area of the brain implicated in schizophrenia,[2] with accumulating evidence that endocannabinoid system dysfunction is likely to play a role in this condition.[3] Remember that if the endocannabinoid system is not functioning properly, the brain cannot balance the hyperactivity of the involved neurotransmitters, which results in an imbalance in the messages that brain cells are sending to each other. There are also numerous studies that report that schizophrenia is likely an inflammatory illness.[4];[5];[6];[7]

The mainstay of treatment for patients with schizophrenia is antipsychotic medications. These drugs have been shown to be effective in reducing the positive symptoms of schizophrenia but do not appear to help with the negative symptoms or the cognitive symptoms. Additionally, antipsychotic medications have numerous side effects that can become intolerable, causing patients to discontinue use. Approximately one third of patients are treatment-resistant, meaning they have not responded to two or more medications.

Recent research reveals that CBD is antipsychotic and that THC may be (but not always) pro-psychotic.

- In a double-blind controlled clinical trial, CBD significantly reduced acute psychotic symptoms after two and four weeks of treatment when compared to baseline. In this trial CBD did not differ from an atypical antipsychotic except for a lower incidence of side effects.[8]
- In a hair analysis for use of cannabinoids and relationship to psychotic symptoms, the THC only group showed higher levels of positive schizophrenia-like symptoms, compared with the no cannabinoid and THC+CBD groups, and higher levels of delusions compared with the no cannabinoid group.[9]
- Cannabidiol was found to exert clinically relevant antipsychotic effects

that are associated with marked tolerability and safety, when compared with current medications. The mechanism by which CBD lessened psychotic symptoms is thought to be due to inhibition of the enzyme that breaks down the endocannabinoid anandamide.[10]

There is some evidence that prolonged use of high potency THC use in teenagers with a genetic predisposition for psychiatric disease may increase the risk of schizophrenia.[11] A very recent study found that young cannabis users aged 16-23 years who had a variation in their AKT1 gene were more likely to have an acute psychotic response to cannabis.[12]

I have a small number of patients with schizophrenia in my practice who are using THC-rich cannabis with good results, but they are selective in choosing cannabis that is sedating and calming. Helpful terpenoids are myrcene, limonene and linalool. Others are using CBD-rich cannabis with reports that they experienced fewer hallucinations and delusions, had improved mood and much less anxiety. I have a number of patients who are using both cannabis and antipsychotic medications, finding that cannabis minimizes the side effects of the pharmaceuticals while treating breakthrough anxiety and insomnia. A few patients are managing symptoms with cannabis treatment alone.

Sources

[←1]

Werner, Felix-Martin, and Rafael Coveñas. "Classical Neurotransmitters and Neuropeptides Involved in Schizophrenia: How to Choose the Appropriate Antipsychotic Drug?." *Current Drug Therapy* 8.2 (2013): 132-143.

[←2]

Glass, M., R. L. M. Faull, and M. Dragunow. "Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain." *Neuroscience* 77.2 (1997): 299-318.

[←3]

Leweke, F. M., et al. "Elevated endogenous cannabinoids in schizophrenia." *Neuroreport* 10.8 (1999): 1665-1669.

[←4]

Hanson, Daniel R., and Irving I. Gottesman. "Theories of schizophrenia: a genetic-inflammatory-vascular synthesis." *BMC Medical Genetics* 6.1 (2005): 7.

[←5]

Coelho, Fernanda Matos, et al. "Increased serum levels of inflammatory markers in chronic

institutionalized patients with schizophrenia." *Neuroimmunomodulation* 15.2 (2008): 140-144.

[←6]

Drexhage, Roosmarijn C., et al. "The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder." (2010): 59-76.

[←7]

Sommer, Iris E., et al. "Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis." *The Journal of clinical psychiatry* 73.4 (2012): 414-419.

[←8]

Leweke, F. M., et al. "Cannabidiol as an antipsychotic: a double-blind, controlled clinical trial on cannabidiol *vs* amisulpride in acute schizophrenics." *2005 Symposium on the Cannabinoids*, Burlington, Vermont, International Cannabinoid Research Society.

[←9]

Morgan, Celia JA, and H. Valerie Curran. "Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis." *The British Journal of Psychiatry* 192.4 (2008): 306-307.

[←10]

Leweke, F. M., et al. "Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia." *Translational psychiatry* 2.3 (2012): e94.

[←11]

Di Forti, Marta, et al. "High-potency cannabis and the risk of psychosis." *The British Journal of Psychiatry* 195.6 (2009): 488-491.

[←12]

Morgan, C. J. A., et al. "AKT1 genotype moderates the acute psychotomimetic effects of naturalistically smoked cannabis in young cannabis smokers." *Translational Psychiatry* 6.2 (2016): e738.

Sue's Story

A year ago, Denise brought her mother Sue in to my office. A tiny Asian lady with immaculate dress, makeup and hair, Sue was very quiet and her daughter did all the talking. They had come to see whether cannabis might help Sue. Denise appeared to be a happy, articulate woman who cared deeply for her mother, but she expressed doubts about using cannabis. Given the level of desperation they both felt, she was open to trying it.

Denise was about five years old when she first knew her mother Sue was different than other mothers. She and her two sisters remember their mother storming out of the room, believing people were talking about or laughing at her, despite there being no one in the room. The girls learned their mother had a traumatic childhood with an abusive father, that she had left school to care for brothers and sisters, that one of her sisters died and that she herself nearly died from scarlet fever. Their father met Sue when he was in the Air Force. He and the children learned to tolerate Sue's delusions.

It wasn't until Denise turned 20 years old that she decided to do something to help her mother. She knew her father wasn't capable of taking care of Sue's increased paranoia, so she pursued a psychologist and eventually a psychiatrist, and her mother was placed on medications after the diagnosis of paranoid schizophrenia was made. The family agreed that the therapists assigned to their mother were great, but Sue always stopped going to appointments and stopped taking the medications only to have the delusions appear again. The drugs made her gain weight and she never felt comfortable taking them. She said that she didn't feel like herself on them.

A devout Catholic, Sue prayed all the time and took care of herself by eating well, exercising and taking care of her body. Despite her struggles with delusions, she managed to cope on her own over the years, even working as an assembler of computer chips in an aerospace factory. The work helped her focus on something other than the delusions. Her employers loved Sue because she worked so hard, but despite their support, she continued to have challenges, sometimes believing that others were whispering about and plotting against her.

When she developed glaucoma, she refused to seek medical assistance, convinced that the voices were responsible for what was happening to her. She said that these voices were physically harming her, taking nutrients away from her body and causing her pain. She was forced to quit her job, still didn't seek medical assistance and finally lost partial sight. She was heartbroken when she lost her job and tried to fill the hours with hobbies to stay busy, but her attempts to stay social were often stymied by the voices she experienced every day.

I started Sue on low dose CBD-rich oil, and slowly increased the dosage with the goal of finding the dose that would mitigate her symptoms. Although she continued to have some delusions, she reported feeling "more in control" and that for the first time in her life she wasn't just passing time until she died, but, rather, really "living." She felt calmer and able to handle the delusions that she continued to have during the day, reporting to me that they didn't bother her as much.

During the night, delusions continued to aggravate her with symptoms that were both physical and painful. We added THC oil at night and experimented with the dosing until Sue began sleeping without waking up multiple times. The increased sleep made a huge difference for her in the day. Denise reported that her mother felt the positive effects of the THC within a week. Sue said "the voices" left her alone and that she was able to stay at home by herself, content. Although THC may cause increased anxiety and paranoia for some suffering with schizophrenia, starting at very low doses, restricting THC use to nighttime only and continuing CBD concurrently has worked well for Sue. Additionally we are experimenting with higher doses of CBD oil during the day to see if we can find a dose that completely eradicates the delusions. Sue reports that she has not experienced any negative side effects from either oil.

Denise and her sisters are feeling huge relief for the improvements in their mother. While their relationships with Sue are complicated because of Sue's psychiatric history, they all notice the positive changes in her behavior and feel more at ease. Denise says, "I've always felt really responsible for my mother as far as being a caregiver, but we've kept a space between us because it's always sort of dangerous to get too close to one another. With cannabis and this positive change, I feel like we've both entered that space and feel its safety. We can now get to know each other better. My mother is now living to live."

Skin Disorders

Both types of cannabinoid receptors have been found throughout the structure of human skin. The role of the endocannabinoid system in skin is thought to regulate cell growth, wound healing and the differentiation of keratinocytes, the cells that make up the different skin layers. Since the endocannabinoid system plays a large part in the immune response, cannabis medicine as treatment for inflammatory skin conditions has been the focus of recent research.[1]

There is evidence that allergic skin conditions, such as contact dermatitis, can be lessened by targeting the endocannabinoid system.[2] Pruritis, the unpleasant sensation of itchiness that leads to excessive scratching, can be difficult to treat. A study of 2,500 patients with allergic eczema showed topical treatment with a cream containing the cannabinoid N-palmithylethanolamide (PEA) significantly decreased symptoms and was well tolerated. Resolution of pruritis occurred in 38%, with significant improvement in a further 41% of the patients.[3] Three other studies using creams containing the same and additional cannabinoids found similar findings, with resolution or significant reduction of symptoms without any adverse side effects.[4,5,6]

Anti-tumor effects have been documented for malignant cancers of the skin.[7] Melanoma cells have been found to express both cannabinoid receptors, and studies have shown the use of cannabinoids decreased the number of viable melanoma cells in the laboratory.[8] Cannabinoid receptors are also expressed in benign papillomas and in malignant squamous cell carcinomas.[9] Malignant tumors treated with cannabinoids showed inhibition of growth, increased apoptotic cells (dying cells) and impaired blood flow.[10]

Patients are using topical cannabis preparations for inflammatory skin conditions, pain, pruritis and skin tumors. Some patients use other delivery methods as well, with sublingual CBD-rich oils for inflammation and inhaled THC for quick relief of pruritis being the most common. The terpenoids β-caryophyllene and pinene are both anti-inflammatory and should be included for enhanced results.

Sources

[←1]

Kupczyk, Piotr, Adam Reich, and Jacek C. Szepietowski. "Cannabinoid system in the skin–a possible target for future therapies in dermatology." *Experimental dermatology* 18.8 (2009):

669-679.

[←2]

Karsak, Meliha, et al. "Attenuation of allergic contact dermatitis through the endocannabinoid system." *science* 316.5830 (2007): 1494-1497.

[←3]

Eberlein, B., et al. "Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study)." *Journal of the European Academy of Dermatology and Venereology* 22.1 (2008): 73-82.

[←4]

C Szepietowski, Jacek. "Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study." *Acta Dermatovenerologica Croatica* 13.2 (2005): 0-0.

[←5]

Szepietowski, Jacek C., Adam Reich, and Tomasz Szepietowski. "Emollients with endocannabinoids in the treatment of uremic pruritus: discussion of the therapeutic options." *Therapeutic Apheresis and Dialysis* 9.3 (2005): 277-279.

[←6]

Stander, S., et al. "Topical cannabinoid agonist. An effective new possibility for treating chronic pruritis." Hautarzt (2006): 57: 801-807.

[←7]

Sarfaraz, Sami, et al. "Cannabinoids for cancer treatment: progress and promise." *Cancer research* 68.2 (2008): 339-342.

[←8]

Blázquez, Cristina, et al. "Cannabinoid receptors as novel targets for the treatment of melanoma." *The FASEB journal* 20.14 (2006): 2633-2635.

[←9]

Casanova, M. Llanos, et al. "Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors." *Journal of Clinical Investigation* 111.1 (2003): 43.

[←10]

Ibid.

Sleep Disorders

Sleep disturbance is one of the main reasons patients come to my office. Poor sleep leads to anxiety, depression, poor memory, anger, increased risk of accidents and increased risk of cardiovascular diseases and death. All of these conditions disrupt quality of life and interfere with the ability to function well at work and at home.

Many people suffering with sleep difficulty will try over-the-counter sleep aids and often seek prescription sleep medications. Unfortunately, research shows that taking hypnotics (sleep-aids) is associated with a greater than threefold increased risk of death even when only 18 doses per year are used.[1]

Limited research into cannabis use and sleep has reported mixed findings and various effects of cannabinoid administration on different aspects of sleep.[2] How cannabinoids affect the stages of sleep and the long-term effects of using cannabis for sleep is still unknown.

That being stated, I have seen thousands of patients who report better sleep with cannabis use. Many of these patients suffer with pain, chronic illness and often anxiety, but I have also successfully treated patients with primary insomnia, sleep apnea, restless leg syndrome, nightmares and bruxism. Patients who report better sleep with cannabis use tell me they have quicker onset of sleep and are able to stay asleep through the night. They report that they feel well rested upon awakening and for the most part, do not experience morning grogginess.

THC and terpenoids, such as myrcene and linalool, are sedating for most people. Patients are using various methods to achieve better sleep. Inhalation or sublingual use of THC-rich cannabis helps with the onset of sleep. Ingestion of cannabis edibles often will prevent waking in the middle of the night due to their longer lasting effects. Lower doses appear to work best for most, as higher doses can be too psychoactive and may stimulate the mind. Many experts recommend taking cannabis 1-2 hours before you plan to go to sleep, as the sedating properties are likely to set in in this time frame. Experimenting with the different methods and timing will help you find what works.

In my experience, patients who are regularly using sleeping pills, who then found that THC-rich cannabis helped with sleep, may experience rebound insomnia when trying to wean themselves off the pills. You may misinterpret the rebound symptoms as an ineffective THC effect, thinking that THC stopped working. The poor sleep is likely due to your brain adjusting to the lack of sleeping pills. With time this will resolve, especially if cannabis is effective for you. I have witnessed thousands of patients discontinue the use of

sleeping pills and have improved quality of sleep with cannabis, without any adverse side effects.

Be aware that CBD in low doses is alerting (but not for everyone), and in higher doses can be sedating. These effects vary person to person. Some patients report not feeling either alert or sedated with CBD. If you are using CBD for another condition, you may want to avoid taking it right before bedtime as it can interfere with sleep in some patients. Once you see how it affects you, you can adjust the timing so that it does not adversely interfere with sleep.

Sources

[←1]

Kripke, Daniel F., Robert D. Langer, and Lawrence E. Kline. "Hypnotics' association with mortality or cancer: a matched cohort study." *BMJ open* 2.1 (2012): e000850.

[←2]

Gates, Peter J., Lucy Albertella, and Jan Copeland. "The effects of cannabinoid administration on sleep: a systematic review of human studies." *Sleep medicine reviews* 18.6 (2014): 477-487.

Spinal Cord Injury

As with numerous other conditions, scientific research of the effectiveness of cannabis for patients suffering spinal cord injuries is lacking. However, there are anecdotal reports of improvement of pain, spasticity, muscle spasms, bladder problems and sleep in patients suffering spinal cord injury.[1,2]

In a 2007 study of 25 patients with spinal cord injury receiving either oral THC or rectal THC-hemisuccinate, there was a significant decrease in spasticity scores and the researchers concluded, "THC is an effective and safe drug in the treatment of spasticity. At least 15-20mg per day were needed to achieve a therapeutic effect."[3] A report of 11 patients with spinal cord injury given a synthetic cannabinoid, Nabilone, also found significant reduction of spasticity.[4]

A number of my patients with spinal cord injury report that they find relief of pain, spasticity and insomnia with cannabis use. These patients often struggle to maintain quality of life and often go through bouts of anxiety and depression.[5] Many report that they began using cannabis to treat the physical symptoms of their injury but find that they achieved an added benefit of a psychological sense of well being with cannabis use.

Patients with spinal cord injury are finding relief with THC-rich cannabis and combination CBD+THC medicine based on personal preference and response. Most prefer to inhale due to the rapid onset with quick relief of spasticity and pain although a few of my patients have found relief with sublingual tinctures and/or edibles. I encourage patients with cervical or thoracic level injuries who want to inhale to use vaporizers as they are at increased risk for pulmonary infections. Terpenoids that are relaxing and sedating, such as linalool and myrcene, can be helpful for spasticity, anxiety and sleep.

Sources

[←1]

Institute of Medicine. The medical value of marijuana and related substances. Marijuana and medicine: Assessing the science base. Joy, J. E., Watson, S. J., and Benson, J. A. Washington, DC: National Academy Press, 1999.

[←2]

Malec, J., Harvey, R. F., and Cayner, J. J. (1982). Cannabis effect on spasticity in spinal cord injury. Arch.Phys.Med.Rehabil. 63: 116-118.

[←3]

Hagenbach, U., et al. "The treatment of spasticity with Δ9-tetrahydrocannabinol in persons with spinal cord injury." *Spinal Cord* 45.8 (2007): 551-562.

[←4]

Pooyania, S., Ethans, K., Szturm, T., Casey, A. and others. (2010). A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Arch.Phys.Med.Rehabil. 91: 703-707.

[←5]

Mann, R., et al. "Burden of spinal cord injury-related neuropathic pain in the United States: retrospective chart review and cross-sectional survey." *Spinal Cord* 51.7 (2013): 564-570.

Andrew's Story

It's pitch dark outside at 3:00 in the morning when Andrew gets up to go to work as a clerk on the docks at Long Beach. He won't have to report in for another five hours, but Andrew is paralyzed from the nipples down, so it takes that long to get ready. No stranger to pain, Andrew initially injured himself while working on the docks with shipping containers, had surgery on his back to fuse two vertebrae and was declared disabled. He could feel the screws moving back then and the pain was near-constant, but morphine and Percocet only made him anxious. Pain medication felt like a Band-Aid, so Andrew got used to pain.

Andrew is a single father of four children and loved tinkering and riding ATVs with them. Two years after his back surgery, while traveling on a country fire road in canyon country with his kids, his vehicle hit a rut, wobbled and then hit a cow fence. The ATV stopped, but he kept going. He was airlifted from the site and learned soon after that he was paralyzed from the nipples down.

"I'm not dead," Andrew stated, despite the paralysis. His arms still worked, so he went back to work as a clerk. The hours it took to get ready to go to work on the docks were often filled with pain. He had developed digestive problems because of the paralysis and experienced a considerable amount of nausea, pain and anxiety daily. Some days his stomach hurt so much that he had to leave work early. He could barely eat. His back constantly seized up and contracted. If you touched his skin, he might feel nothing, but internally he could feel it as it deflected to his stomach. His kids noticed, winced at his pain, but learned to live with it just as he did.

The doctors prescribed many different medications, but they made him even more depressed and increased his anxiety. He continued to try various prescriptions, determined to be present and a good father for his kids, but the ten medications that he was prescribed, along with probiotics and many OTC medicines, only made him feel worse.

Andrew knew nothing about the medicinal value of cannabis and had even tried Marinol (synthetic THC available with a prescription) with no effect. He was dubious that medical cannabis would do anything for his constant pain and nausea but he decided to try it. It has changed his life. Both inhaling it and taking cannabis edibles have helped to lessen the stomach issues and the anxiety. He reports that he is able to eat, his back spasms are improved and his anxiety has lessened considerably. Cannabis even helps ease the severe and debilitating pain he's had in his left hip ever since the accident.

Andrew uses his cannabis medicine before work and then later at his lunch break and when he gets home. Far more independent, he is able to stretch

every day and perform a series of exercises to keep him strong. His children have noticed. They've witnessed his pain and problems and see how much the cannabis helps him. Andrew and his kids have a mission-like intensity about educating the public on the medicinal value of cannabis.

Getting up in the dark hours before dawn, Andrew is determined to be as hard working and independent as he's ever been. He has had great results and has overcome many obstacles. He wants to change the stigma around cannabis and share how it's improved the quality of his and his family's life.

Tourette Syndrome

Tourette syndrome (TS) is a neurological disorder manifested by repetitive, involuntary movements and vocalizations called tics. The disorder is named for Dr. Georges Gilles de la Tourette, the French neurologist who first described the condition in an 86-year-old French noblewoman in 1885.

The cause of TS is still unknown. Recent research points to genetic causes with about a 50% chance of parents passing the gene on to their children. Abnormalities in certain brain regions, including the basal ganglia, cortex and frontal lobes and in the neurotransmitters dopamine, serotonin, and norepinephrine have been found in persons suffering with TS and are a focus of current research.

Many patients who suffer with TS are finding relief of their symptoms with cannabis. A large percentage of people who have been diagnosed with TS also suffer with other significant conditions, such as OCD, ADHD, mood disorders and anxiety.

The conventional medications used to treat these conditions are not always helpful and often cause a wide array of unwanted side effects. Researcher Kirsten Müller-Vahl and her group at Germany's Medical School of Hanover reported in 1998 that 82% of TS patients who reported prior use of cannabis experience a "reduction or complete remission of motor and vocal tics and amelioration of premonitory urges and OCD symptoms."[1] In 1999, the same researchers reported successful treatment of a 25 year-old male with Tourette syndrome who received a single dose of 10mg of THC with reduction of tic severity score from 41 pre-THC to 7 post-THC treatment.[2]

Müller-Vahl's group went on to do a number of studies on the use of cannabis to treat Tourette syndrome. She published results in 2003, looking at a single-dose in 12 patients followed by a six week, randomized trial in 24 patients and found that "THC reduces tics in TS patients without any serious adverse side effects and no impairment on neuropsychological performance."[3]

Most of my patients with TS have tried pharmaceuticals and either found them to be ineffective or found them to have too many negative side effects. The adult patients in my practice are using mainly THC-rich cannabis products to help decrease the number of tics and other symptoms of TS and its related conditions, and they report no adverse side effects and improved quality of life. A small number of pediatric patients brought for evaluation after trying pharmaceuticals that caused adverse side effects and/or were uneffective, have responded successfully to high CBD:THC ratio treatment of their TS symptoms.

Sources

[←1]

Müller-Vahl, K. R., et al. "Cannabinoids: possible role in patho-physiology and therapy of Gilles de la Tourette syndrome." *Acta Psychiatrica Scandinavica* 98.6 (1998): 502-506.

[←2]

Müller-Vahl, K R., et al. "Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol." *American Journal of Psychiatry* 156.3 (1999): 495-495.

[←3]

Müller-Vahl, Kirsten R. "Cannabinoids reduce symptoms of Tourette's syndrome." *Expert Opinion on Pharmacotherapy* 4.10 (2003): 1717-1725.

Jacob's Story

My immediate impression of the slight, beautiful woman and the tall, thin boy with her was that their mother/child bond was extraordinary, a far different relationship than you generally see between a parent and an adolescent. I was soon to learn that bond had come at great cost to both Randi and her son, Jacob.

Jacob's father died when he was 10 years old after a vicious bout with cancer, and the tics that had plagued him when he was younger came back. Jacob had always been a complicated kid, diagnosed with both Asperger syndrome and Tourette syndrome. But the anxiety and stress of the trauma of watching his father die, as well as the onset of puberty eventually made his symptoms unmanageable, and his mother had to pull him out of school. While pharmaceuticals helped for a bit, the effects soon wore off and she was loathe to put her son on the anti-seizure meds the neurologist prescribed because she'd read so much about their negative side effects.

After seeing a documentary about a young man with a tic disorder who found relief with cannabis, they began their journey by investigating cannabis and coming to see me. Jacob was fourteen by then and his mother said his body shook the car when he had tics.

He began using CBD oil with a CBD:THC ratio of 24:1 and saw immediate results. His vocal and motor tics improved, as did his tremors and self-injurious behaviors. The frequent headaches that he'd experienced also disappeared and for a period of six weeks he was tic-free. When some of his behaviors and tics started up again, we began tinkering with the dosage, and now we're experimenting with different products.

Overall, Randi believes that Jacob has seen an 80% improvement and while Jacob finds it difficult to describe the effects of cannabis on his mental health, he says he just "feels better." He's had no meltdowns and is managing life. In fact, Randi says she has her son back. "Cannabis is the something out there that has given my son his life back without turning him into a zombie. He would have lost it otherwise."

Traumatic Brain Injury

Traumatic Brain Injury (TBI) occurs when an external force delivers a violent blow to the head, resulting in brain dysfunction. Blunt force trauma, penetrating injury and a severe skull fracture can cause TBI. TBI may be mild, with temporary brain damage, or may be quite serious, causing permanent and long-term complications and death.

The symptoms of TBI vary widely and can include headache, nausea or vomiting, fatigue, difficulty sleeping, loss of balance, sensitivity to light or sound, seizures, communication problems, memory or concentration problems, mood swings, feeling depressed and/or anxious, slurred speech, agitation and combativeness. TBI has been linked to dementia and chronic neurodegenerative changes in the brain. TBI interferes with quality of life for both the patient and his or her loved ones.

After initial treatment and stabilization of the head injury, most patients with TBI must go through rehabilitation to relearn basic life functions and how to perform daily activities. These patients often end up on multiple medications, such as sleeping pills, antidepressants, anti-anxiety medications, mood stabilizers, anticonvulsants, pain relievers and antipsychotics.

According to recent research, chronic traumatic brain inflammation, also called chronic traumatic inflammatory encephalopathy, is a major contributing factor to post-traumatic neurodegeneration. Cannabinoids are proven neuroprotective agents with potent anti-inflammatory properties and are being researched as potential treatment for TBI patients. Unfortunately, human research is limited but animal studies are promising.

- Endocannabinoids are significantly increased immediately after brain injury, suggesting that they have a neuroprotective role.[1,2,3]
- Endocannabinoids are found to decrease the intensity and duration of toxicity to brain cells after induced chemical damage.[4,5,6]
- Endocannabinoids lessen the inflammatory process and enhance brain cell survival after injury.[7,8,9,10,11]
- Synthetic cannabinoids given to animals with brain injury protected against brain cell death and injury in multiple studies.[12,13,14,15]
- Cannabidiol (CBD) given immediately after oxygen and blood flow were cut off reduced neuronal injury, cerebral hemodynamic impairment, brain edema and seizures and restored motor and behavioral performance in the 72 hours after the insult.[16]

In the only human data looking at the relationship between cannabis and TBI, a 3-year retrospective review revealed that a positive THC screen was associated with decreased mortality in adult patients sustaining TBI; mortality of patients with positive THC test was 2.4% and with a negative THC test was 11.5%.[17]

In my clinical experience, patients with TBI benefit greatly with the use of cannabis. Patients report relief of pain, enhanced sleep, less agitation, and mood stabilization. They report no adverse side effects from cannabis use and are able to discontinue most, if not all, pharmaceuticals. Depending on personal preference, some are using only CBD-rich cannabis and others are using combination CBD+THC cannabis. I encourage all of my patients with TBI to include CBD rich cannabis in their regimen.

Sources

[←1]

Berger, Christian, et al. "Massive accumulation of N-acylethanolamines after stroke. Cell signaling in acute cerebral ischemia?." *Journal of neurochemistry* 88.5 (2004): 1159-1167.///

[←2]

Hansen HH, Ikonomidou C, Bittigau P, et al. Accumulation of the anandamide precursor and other N-acylethanolamine phospholipids in infant rat models of in vivo necrotic and apoptotic neuronal death. J Neurochem 2001;76:39–46.///

[←3]

Panikashvili, David, et al. "An endogenous cannabinoid (2-AG) is neuroprotective after brain injury." *Nature* 413.6855 (2001): 527-531.

[←4]

Kim SH, Won SJ, Mao XO, et al. Molecular mechanisms of cannabinoid protection from neuronal excitotoxicity. Mol Pharmacol 2006;69:691–6///

[←5]

Marsicano G, Goodenough S, Monory K, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science 2003;302:84–8///

[←6]

van der Stelt, Mario, et al. "Acute neuronal injury, excitotoxicity, and the endocannabinoid system." *Molecular neurobiology* 26.2-3 (2002): 317-346.

[←7]

Klein, Thomas W. "Cannabinoid-based drugs as anti-inflammatory therapeutics." *Nature Reviews Immunology* 5.5 (2005): 400-411.//Murikinati S, Juttler E, Keinert T, et al. Activation of cannabinoid 2 receptors protects against cerebral ischemia by inhibiting neutrophil recruitment. FASEB J 2010;24:788–98.///

[←8]

Walter, Lisa, and Nephi Stella. "Cannabinoids and neuroinflammation." *British journal of pharmacology* 141.5 (2004): 775-785.//Guzmán, Manuel, Cristina Sánchez, and Ismael Galve-Roperh. "Control of the cell survival/death decision by cannabinoids." *Journal of Molecular Medicine* 78.11 (2001): 613-625//

[←9]

Galve-Roperh, Ismael, et al. "Mechanisms of control of neuron survival by the endocannabinoid system." *Current pharmaceutical design* 14.23 (2008): 2279-2288.///

[←10]

Ramirez, Servio H., et al. "Activation of cannabinoid receptor 2 attenuates leukocyte–endothelial cell interactions and blood–brain barrier dysfunction under inflammatory conditions." *The Journal of Neuroscience* 32.12 (2012): 4004-4016./// 11

[←11]

Viscomi MT, Oddi S, Latini L, et al. Selective CB2 receptor agonism protects central neurons from remote axotomy-induced apoptosis through the PI3K/Akt pathway. J Neurosci 2009;29:4564–70

[←12]

Alonso-Alconada, D., et al. "The cannabinoid WIN 55212-2 mitigates apoptosis and mitochondrial dysfunction after hypoxia ischemia." *Neurochemical research* 37.1 (2012): 161-170.

[←13]

Alonso-Alconada D, Alvarez FJ, Alvarez A, et al. The cannabinoid receptor agonist WIN 55,212-2 reduces the initial cerebral damage after hypoxic-ischemic injury in fetal lambs. *Brain Res* 2010;1362:150–9.

[←14]

Fernández-López, David, et al. "The cannabinoid agonist WIN55212 reduces brain damage in an in vivo model of hypoxic-ischemic encephalopathy in newborn rats." *Pediatric research* 62.3 (2007): 255-260.

[←15]

Fernández-López, David, et al. "The cannabinoid WIN55212-2 promotes neural repair after neonatal hypoxia–ischemia." *Stroke* 41.12 (2010): 2956-2964.

[←16]

Lafuente H, Alvarez FJ, Pazos MR, et al. Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs. Pediatr Res 2011;70:272–7.

[←17]

Nguyen, Brian M., et al. "Effect of marijuana use on outcomes in traumatic brain injury." *The American Surgeon* 80.10 (2014): 979-983.

Brian's Story

Brian and his wife are a young and attractive couple in their thirties. When when they came in to visit me for the first time, their anxiety was palpable. I learned that desperation had propelled them into my office and that both were hopeful for good results despite years of dealing with Brian's serious condition.

They live in the suburbs with their two young children and have a baby on the way. Brian is only 37 years old but is already a retired police officer. His journey to my office began when he became a police officer in 2001. He loved his job and believed himself to be very good at it. He was awarded Officer of the Year twice, worked in a helicopter for years and was on the SWAT team.

Early one evening in 2008, he and his partner noticed a wanted suspect riding a bicycle. Brian was driving the car, training his partner who was sitting in the seat next to him. Brian pulled the car over and his partner jumped out to chase the suspect who by then had jumped off the bicycle and run. Brian parked the car, jumped out and began running after the suspect as well but stopped at a curb where trash cans and dusk obscured the view of a young driver going to bible study. Brian was hit head-on and flung onto the hood of the car.

Despite a community hospital right down the street from the accident, Brian's injuries warranted a trauma center, so he was transported, already unconscious and in a coma, to a medical facility further away. Brian's family was told he had suffered major head trauma and the injury was critical enough to threaten his life. He remained in a coma for 16 days and, when he awoke, he had no memory of much of his life, including his friends and family.

He was transferred to a rehab center and worked for the next 18 months on regaining basic life skills – walking, speaking, basic arithmetic and reading. While he had support from friends and police officers, he shared with me how incredibly difficult it was to get better. "Better" for Brian meant that he was relearning basic life skills and making new memories.

The rehab center was wonderful and helped him profoundly, but when he was discharged, he was on five medications. He had significant back pain and was given pain medication. He also lost eyesite as a result of the brain injury and was diagnosed with legal blindness. The police department retired him as a police officer, which plunged him into depression, so he began taking medication for that too.

He did what he was told, but with the support and input of his new wife, a practicing nurse, he decided he was too young to be on so many medications. They were worried about the long-term effects of the medication on his body, particularly on his liver, which they both knew metabolized many of the drugs. The weaning process was difficult and Brian suffered from terrible pain and

mood swings. That's when a friend who worked for a local cannabis producer recommended he try cannabis medicine.

As a police officer, all Brian had ever learned or knew about cannabis was negative. He was desperate and listened to his friend who began educating him about medical cannabis. When he and his wife finally came to visit me, they were nervous but willing and ready to try it. I recommended he start with a CBD-rich tincture. Brian reported that within one week, he felt different. His mood swings lessened considerably, and he felt dramatically less pain. "It was a godsend for me," he said.

He has weaned himself from seven pharmaceuticals and continues to tinker with various products and dosages of CBD and THC. He takes oil in a high CBD:THC ratio twice a day and says that he feels the closest to his pre-brain injury self as he's ever felt, and his wife notices the dramatic change as well. He has also become a vocal advocate for medical cannabis, committed to educating people and erasing the stigma around it. He has been honest with his family and friends and they have, for the most part, been supportive because they see the difference it has made on his quality of life.

Brian wants to get back to work and apply for a job, but he's concerned about applying to those companies who require drug testing. It's frustrating to him that the legal system of which he has been such an integral part isn't as educated as they might be regarding the beneficial effects of cannabis. Brian is determined to teach them otherwise.

Appendix A: History of Cannabis Timeline

The history of cannabis and its path to illegality is fascinating. The plant was cultivated in Asia over 10,000 years ago and its use as a medicine has been well documented. Here is a timeline that highlights important dates:

2350 B.C.: Oldest written description of cannabis in the *Pyramid Texts* from Egypt.

1700 B.C.: Cannabis is described in the medical papyri in Ancient Egypt and Mesopotamia (*Papyrus Ramesseum III* and *Ebers Papyrus*) as a treatment for eye conditions, female disorders, migraine headaches and toenail conditions.

440 B.C.: Herodotus wrote about Scythians using cannabis during funeral rites.

1st Century C.E.: Legendary emperor of China, Shen-Nung, writes about herbal remedies in the *Pen-ts'ao*, where cannabis was recorded as a treatment for pain associated with gout and arthritis.

350 C.E.: Traces of hashish (concentrated cannabis resin) were found with the remains of a young woman who died in childbirth; cannabis is thought to have been used to ease the labor of childbirth.

1542: *Cannabis sativa* is named by German physician and botanist Leonhart Fuchs in his book *De Historia Stirpium.*

1600s: Cannabis used for sleep, dysentery, appetite, headaches and digestive problems in India.

1798: Napolean's soldiers bring hashish from Egypt back to France where it becomes a focus of study by scientists for its pain-relieving and sedative properties.

1833: Irish physician Dr. William O'Shaughnessy travels to India where he witnesses cannabis being used for arthritis, rabies, cholera and convulsions.

1842: Dr. O'Shaughnessy brings cannabis back to Europe, where it becomes popular for treatment of depression, asthma, migraine headaches, "female disorders", nerve pain and muscle spasms.

1840s: Tincture of cannabis (cannabis in alcohol) becomes available in Europe and in the United States.

1840-1900: Numerous reports of the therapeutic and medicinal benefits of

cannabis published in the medical literature.

1911: The state of Massachusetts passes a law making it illegal to sell or possess cannabis and other "hypnotic" drugs without a prescription; New York and Maine follow suit in 1914. Between 1915 and 1927, eight more states pass anti-cannabis laws.

1936: The film *Reefer Madness* is released in 1936 to warn parents about the dangers of cannabis use, brainwashing an entire generation with misinformation.

1937: Henry Anslinger, the first commissioner of the US Federal Bureau of Narcotics, gets the federal Marijuana Tax Act of 1937 passed. Taxes were placed on anyone who wanted to use hemp industrially or cannabis medically; those who did not comply were fined heavily or jailed for tax evasion.

1938: New York's Mayor Fiorello LaGuardia appoints a committee of scientists to assess the medical, sociological and psychological aspects of cannabis use in New York City.

1941: Cannabis is removed from the US Formulary and is no longer available for medical use.

1944: Mayor Fiorello's study of cannabis reports no proof of major crime associated with cannabis, no association with aggression or antisocial behavior, no evidence of personality change or sexual overstimulation. The study was denounced and ignored.

1951: Congress passes the Boggs Act, which sets harsh mandatory sentences for violations of the Marijuana Tax Act.

1964: Israeli researchers isolate and identify delta-9-tetrahydrocannabinol as the psychoactive compound in the cannabis plant.

1970: Congress and President Nixon pass the Controlled Substance Act into law, and placed cannabis into the most restrictive category, Schedule I, pending completion of further studies, to be done by the Shafer Commission. The Commision recommended that cannabis should be reclassified and prohibition ended. Nixon ignored these recommendations.

1972: NORML (National Organization for the Reform of Marijuana Laws) launches the first petition to reschedule marijuana from Schedule I to Schedule II. The petition was eventually given a hearing in 1986 and was ultimately denied.

1973: Researchers led by UCLA pulmonologist Dr. Donald Tashkin find that

both smoked cannabis and oral THC cause dilatation of the pulmonary airways, not constriction of the lungs as previously presumed.

1975: Researchers report in the Journal of the National Cancer Institute that some cannabinoids have the ability to shrink tumors in a dose-dependent manner.

1976: Glaucoma patient Robert Randall files a lawsuit against the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), the National Institute on Drug Abuse (NIDA), the Department of Justice (DOJ) and the Department of Health, Education & Welfare, claiming that his cultivation of marijuana for which he was being prosecuted, was a medical necessity. The charges against him were dropped and federal agencies began providing him with FDA-approved medical marijuana. Although he had won this case, government tried to prevent him from gaining legal access to marijuana and after filing another lawsuit in 1978, he gained access to medical marijuana through a federal pharmacy.

Mid-1980's: Randall's case leads to the FDA Compassionate Investigational New Drug program, which allowed 30 patients to receive medical marijuana from the government. The program stopped accepting patients in 1992 after President George H.W. Bush's administration decided to "get tough on drugs."

1988: The DEA's own administrative law judge, Francis L. Young, stated that marijuana "is one of the safest therapeutically active substance known to man…" and recommended that it be reclassified to a Schedule II drug. The DEA responded by setting new criteria for accepted medical use of a drug and refused to reschedule cannabis.

1988: Researchers discover that rats have endogenous cannabinoid receptors, which leads to the mapping of the locations of a cannabinoid receptor system in man in 1990 and the discovery of naturally occurring cannabis-like compounds in the human brain in 1992.

1992: The DEA issues a final rejection of all pending requests to reclassify cannabis.

1996: California becomes the first state to pass a medical marijuana law with voter initiative Proposition 215 getting 55.6% of the vote.

2002: Patients and patient advocates petition the DEA to reschedule cannabis to Schedule III, IV, or V. This was ultimately rejected in 2011.

2010: Oregon reclassifies cannabis at their state level to a Schedule II drug.

2012: Colorado voters pass Amendment 64 with 55.32% of the vote, which allows adults over age 21 to grow and possess marijuana for recreational purposes. Washington voters pass Initiative 502 (getting 56% of the vote), making small amounts of recreational marijuana legal for adults over age 21.

2013: A federal appeals court rejects a petition from three medical cannabis advocacy groups who seek to reclassify cannabis to a different schedule classification.

2014: The Federal Farm Bill passes, otherwise known as the Agricultural Act of 2014, which states that hemp is defined as containing 0.3% THC or less and allows for industrial hemp to be grown in state-sanctioned research programs. This opens the door for industrial hemp entrepreneurs to start selling hemp-derived CBD.

2015: The FDA sends cease and desist letters to numerous companies making medical claims about hemp-derived CBD products after tests reveal that the majority of products do not contain CBD.

2016: As of the writing of this book, there are 28 states with medical cannabis laws and eight states with laws governing recreational use of cannabis.

Appendix B: Effects of Cannabis by Body System

Neurological

- Relaxation and/or Drowsiness (effective for insomnia, anxiety).
- Pain Relief (works synergistically with other pain medications and is especially effective at reducing pain caused by nerve damage and migraine headaches).
- Euphoria (effective for depression).
- Neuro-protectant.
- Anticonvulsant.
- Intensified sensations (enhances taste of food, enhances sexual sensations).

Adverse Side Effects (THC only) can include panic, sadness, poor judgment, difficulty concentrating, impaired memory and decreased coordination.

Respiratory

- Bronchodilator (opens airways in asthmatic patients).

Adverse Side Effects include airway irritation if smoked. Cannabis smoke can include tar, carbon monoxide, acids, aldehydes, pyrobenzenes and other chemicals. Vaporization is a healthier method of inhalation.

Circulatory

- Mild decrease in blood pressure during use.
- Mild decrease in overall blood pressure with long term use.

Adverse Side Effects (THC only) can include a temporary increase in heart rate.

Optical

- Lowers pressure in eyes (effective for glaucoma)

Adverse Side Effects (THC only) can include dry eyes and reddening of whites of eyes.

Muscular-skeletal

- Reduces muscle spasms, spasticity, tics and tremors.
- Reduces ataxia.
- Decreases inflammation in joints (effective for arthritis).

Adverse Side Effects (THC only) can include decreased coordination.

Digestive (Stomach, Small and Large Intestines)

- Reduces intestinal muscle spasms (effective for colitis and IBS).
- Stimulates appetite.
- Decreases nausea and vomiting (effective for chemotherapy and other conditions).
- Decreases intestinal inflammation (effective for colitis).

Immune System

- Suppresses inflammation (effective for arthritis, immune-mediated illnesses).

Possible Side-Effects of Long-Term Heavy THC Use

- Mood disturbance with chronic heavy use of THC (depression, apathy, social isolation).
- Withdrawal symptoms including irritability, insomnia, anxiety and depression. Avoid these long term side-effects by abstaining from cannabis use for 1-2 weeks every 3 months if daily user, or for those who cannot take time off due to severe medical conditions, changing chemovars, CBD:THC ratios or methods of use can help minimize or prevent withdrawal.

Appendix C: Pharmacokinetics of Cannabis

Pharmacokinetics is the branch of pharmacology concerned with the movement of drugs within the body. The pharmacokinetics of cannabis refers to the absorption, distribution and metabolism of the cannabinoids in the human body. Since cannabis can be taken in many ways, the method of delivery will influence how much is absorbed and metabolized. The ways that medical cannabis users take cannabis include inhalation, ingestion, sublingual, topical, rectal and transdermal. This appendix serves as a review of the scientific literature that has explored how cannabis acts in the body once it is taken or applied. Chapter 4 has more details on what a medical patient can expect with the different methods of delivery.

Inhalation

When inhaled, the absorption of THC through the lungs is rapid and levels of THC in plasma can be detected within seconds. The bioavailability (how much of the compound is actually used by the body) of inhaled THC varies from 5-35% due to variables such as dose inhaled, the depth of inhalation and the length of time that the breath is held.[1] Bioavailability of CBD has been measured at approximately 31%.[2] Inhaling cannabis is the most efficient method of delivery and experienced users have been shown to have increased efficiency when compared to occasional users.[3]

Ingestion

Oral ingestion of THC is slow and unpredictable with variable absorption rates based on numerous variables. Stomach contents including gastric acid, dose ingested, the carrier medium, and the presence of other drugs can influence the rate of absorption. Bioavailability is low with oral ingestion and has been documented at 4-20%.[4] Peak plasma levels of THC have been reported between 2-6 hours after ingestion.[5] CBD has similar low bioavailability to THC when orally ingested.[6]

Sublingual

Sublingual administration of THC and CBD has highly variable rates of absorption and is difficult to measure as some of the product may be swallowed which can affect bioavailability. Studies of Sativex$_{TM}$, a sublingual cannabis extract approved in Europe, report excellent bioavailability if the oil is held sublingually and allowed to absorb.[7] The bioavailability of sublingual THC is higher than the bioavailability of sublingual CBD.[8]

Topical

Topical application of cannabinoids is difficult because they are lipophilic (fat-loving) and do not penetrate the deeper layers of the aqueous skin efficiently, however if they are prepared properly, they can have effects at the local application site. Bioavailability studies on topical use of cannabis have not been performed.

Rectal

The pharmacokinetics of rectal administration based on limited studies report that THC by itself is not absorbed rectally.[9] When THC was combined with a chemical compound called hemisuccinate, which was performed in the laboratory and is not currently available to patients, the bioavailability from rectal suppositories is double that of the oral route.[10,11] To date, the only study looking at rectal bioavailability of CBD reported improved colitis symptoms in mice if rectal CBD was given prior to the insult causing the colitis; in this report rectal CBD was more effective than oral CBD at reducing the changes in the gut due to colitis.[12]

Transdermal

The pharmacokinetics of cannabinoid delivery with this method is limited. Likely the hydrophobic (not soluble in water) cannabinoids require the addition of a chemical "permeation enhancer" so that the compounds can penetrate the aqueous layer of the skin to reach the bloodstream. One report of delta-8-THC delivered by transdermal patch in both animals and humans achieved a steady state level in plasma in 1.4 hours and maintained this level for 48 hours.[13] This study also reported that the permeability of CBD and CBN was greater than delta-8-THC.[14] In 2003, Israeli researchers developed a CBD transdermal patch, using an ethosomal system, which is composed of phospholipid, ethanol and water, and allows for diffusion of both hydrophobic and hydrophilic compounds. Testing in rodents showed significant accumulation of the drug in the skin and in the underlying muscle with steady state levels of CBD in plasma achieved by 24 hours and lasting at least 72 hours.[15]

THC Distribution and Metabolism

Since THC is highly lipophilic (fat-loving and not water soluble), after absorption it is initially distributed and taken up by tissues that are highly perfused, such as the heart, lung, brain and liver. Over time, THC redistributes into fatty tissue and may be retained there for some time. THC is broken

down in the liver into numerous compounds. The primary breakdown product is 11-hydroxy-THC, which is psychoactive, sedating and has a longer half-life than THC. The amount of 11-hydroxy-THC formed after inhalation is relatively small, but quite large with oral ingestion of THC, as blood containing absorbed THC from the intestines passes through the liver. This is called the first pass effect. 11-hydroxy-THC is further broken down into THC-carboxylate, which is inactive.

THC and its metabolites are excreted mainly in feces but also in urine and the elimination of one dose of THC from the body takes approximately 3-5 days. THC and its metabolites are stored in the body's fatty tissue. When the metabolites move out of the fat, they bind to a sugar compound and become slightly soluble in water and are then eliminated in feces and urine. The presence of THC and its metabolites in the body's fat tissues have no psychoactive effects. If cannabis is used regularly, the drug will accumulate in the body and will continue to be excreted for months after last use. Studies show that there is extreme variation in excretion patterns for different individuals.[16]

CBD Distribution and Metabolism

CBD like THC is highly lipophilic and is taken up by the brain and adipose tissue. CBD is highly protein bound and about 10% of the absorbed CBD in the body is bound to circulating red blood cells. CBD is metabolized in the liver where it is hydroxylated to 7-OH-CBD by the cytochrome P450 system (mostly CYP3A and CYP2C). This breakdown product is then broken down further in the liver and excreted primarily in feces with some excretion in the urine.[17]

As you can see, the absorption of cannabinoids in the human body is widely varied for each method and also varies significantly person to person. This variability is one of the reasons that most experts advise starting with low amounts of cannabis medicine and increasing slowly to reach the desired effects.

Sources

[←1]

Grotenhermen, F. Pharmacokinetics and Pharmacodynamics of Cannabinoids. Clinical Pharmacokinetics (2003) 42: 327-60

[←2]

Ohlsson A, et al. Single dose kinetics of cannabidiol in man. In Agurell S, Dewey WL, Willette RE (Eds) *The cannabinoids: chemical, pharmacologic and therapeutic aspects.* Orlando: Academic

Press, 1984:219-225

[←3]

Lindgren, Jan-Erik, et al. "Clinical effects and plasma levels of Δ9-tetrahydrocannabinol (Δ9-THC) in heavy and light users of cannabis." *Psychopharmacology* 74.3 (1981): 208-212.

[←4]

Huestis, Marilyn A. "Human cannabinoid pharmacokinetics." *Chemistry & biodiversity* 4.8 (2007): 1770-1804.

[←5]

Ohlsson, A., et al. "Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking." *Clinical Pharmacology & Therapeutics* 28.3 (1980): 409-416.

[←6]

Karschner, Erin L., et al. "Plasma cannabinoid pharmacokinetics following controlled oral Δ9-tetrahydrocannabinol and oromucosal cannabis extract administration." *Clinical chemistry* 57.1 (2011): 66-75.

[←7]

Ibid.

[←8]

Guy, G. W., and P. J. Robson. "A phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK0215)." *Journal of Cannabis Therapeutics* 3.4 (2004): 121-152.

[←9]

Perlin, Elliott, et al. "Disposition and bioavailability of various formulations of tetrahydrocannabinol in the rhesus monkey." *Journal of pharmaceutical sciences* 74.2 (1985): 171-174.

[←10]

Mattes, Richard D., et al. "Bypassing the first-pass effect for the therapeutic use of cannabinoids." Pharmacology Biochemistry and Behavior 44.3 (1993): 745-747.

[←11]

Elsohly, Mahmoud A., et al. "Rectal bioavailability of Δ-9-tetrahydrocannabinol from the hemisuccinate ester in monkeys." *Journal of pharmaceutical sciences* 80.10 (1991): 942-945.

[←12]

Schicho, Rudolf, and Martin Storr. "Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice." *Pharmacology* 89.3-4 (2012): 149-155.

[←13]

Valiveti, Satyanarayana, et al. "In vitro/in vivo correlation studies for transdermal Δ8-THC development." *Journal of pharmaceutical sciences* 93.5 (2004): 1154-1164.

[←14]

Ibid.

[←15]

Lodzki, M., et al. "Cannabidiol—transdermal delivery and anti-inflammatory effect in a murine model." *Journal of controlled release* 93.3 (2003): 377-387.

[←16]

Holubek, W. Medical Risks and Toxicology. In *The Pot Book*, Edited by J. Holland, Park Street Press, 2010.

[←17]

Ohlsson A, et al.

Appendix D: Phytocannabinoids and Their Effects

Phytocannabinoid		Medical Effects	Important Facts
Delta-9-tetrahydrocannabinol	THC	Analgesic Muscle relaxant Anti-anxiety Anti-inflammatory Antioxidant Appetite stimulant Stops nausea and vomiting Induces sleep Anti-tumor Reduces eye pressure	• Most prominent phytocannabinoid, made from heating up THCa • Most psychoactive • Discovered in 1964 • Mimics brain-produced endocannabinoids by binding to cannabinoid receptors • Tolerance can develop with chronic use • Withdrawal can occur with cessation of chronic heavy use
Cannabidiol	CBD	Potent anti-inflammatory Analgesic Antioxidant Muscle relaxant Anti-anxiety Antipsychotic Anti-depressant Anticonvulsant Neuroprotectant Stops nausea and vomiting Anti-tumor Anti-bacterial (potent against MRSA)	• Non-psychoactive • Alerting effect in lower doses, sedating in higher doses • No tolerance or withdrawal • Can be used to treat THC withdrawal • Allows brain-produced endocannabinoids to last longer by inhibiting the enzyme called fatty acid amide hydroxylase ("FAAH") that breaks down the endocannabinoid • Binds to a non-cannabinoid receptor called TRPV-1, which mediates pain and inflammation

			• Binds to 5-HT1A receptor which mediates anxiety • Blocks GPR55 receptor which may decrease cancer cell proliferation and bone reabsorption
Cannabinol	CBN	Analgesic Anti-bacterial (potent against MRSA) Promotes bone growth Reduces eye pressure	• Discovered in 1899 • Breakdown product of THC • CBN content increases as THC degrades over time • Mildly psychoactive • Increases the psychoactivity of THC when both are present • Not present in freshly cut flowers
Cannabigerol	CBG	Anti-bacterial Anti-inflammatory Anti-tumor Anti-anxiety Promotes bone growth Decreases pressure in eyes	• Non-psychoactive • Found in higher amounts in hemp
Cannabichromene	CBC	Analgesic Potent anti-anxiety Anti-inflammatory Anti-tumor Promotes bone growth Anti-fungal Promotes bone growth	• Non-psychoactive • Allows brain-produced endocannabinoids to last longer • Can increase the viability of developing brain cells
Tetrahydrocannabinolic Acid	THCA	Anti-inflammatory Anti-spasmodic Anti-tumor Anti-nausea Possible anticonvulsant	• Non-psychoactive • Main compound in raw (unheated) cannabis flowers • When heated up, THCA changes to THC

Cannabidiolic Acid	CBDA	Anti-inflammatory (selective COX-2 inhibitor) Anti-tumor Inhibits migration of certain breast cancer cells Anti-nausea	• Non-psychoactive • Found in raw (unheated) cannabis flowers • When heated up CBDA changes to CBD
Δ^9-tetrahydrocannabivarin	THCV	Decreases appetite Anticonvulsant Promotes bone growth Anti-anxiety Reduces tremors Analgesic Stimulating effect	• Potent antagonist of cannabinoid receptors • Suppresses THC effects in lower doses but enhances THC effects in higher doses • Decreases the length of time of THC's psychoactive effect • Chemovar called "Doug's Varin" reported to have THC:THCV ratio of ~6:7 and reported to help with PTSD and Parkinson's disease
Delta-8-tetrahydrocannabinol	Δ^8-THC	Stops nausea	• Non-psychoactive
Cannabidivarin	CBDV	Promotes bone growth Anti-convulsant Anti-nausea	• Non-psychoactive
Cannabigivarin	CBGV	Possible pain relief and anti-inflammatory	• Binds to TRPV1 receptors that play a role in pain sensation and inflammation (De Petrocellis 2011)
Cannabigerolic Acid	CBGA	Analgesic Anti-inflammatory Anti-bacterial	• Precursor to THCA and CBDA • Precursor to CBG and CBC

Appendix E: Terpenoids and Their Effects

Terpenoid	Also found in:	Effects	Aroma	Synergistic with:
Limonene	Citrus rinds Caraway seeds Dill seeds Rosemary Juniper Peppermint	Potent anti-depressant Anti-anxiety Anti-tumor Chemotherapeutic (causes breast cancer cells to commit suicide) Active against acne bacteria Suppresses GERD Anti-bacterial/anti-fungal Bronchodilator	Orange Citrus Spicy	CBD – enhanced anti-depressant and anti-anxiety effects CBD & CBG – enhanced anti-cancer effects THC – enhanced anti-GERD effects
β-Caryophyllene *often found in CBD-rich chemovars	Black pepper Cloves Cotton Oregano Hops	Anti-inflammatory Analgesic Gastrointestinal Relief Anti-bacterial Anti-fungal Anti-tumor *Activates the CB2 receptor located in immune system and gut (2008, Gertsch)	Woody Spicy	THC – enhanced gastric cell protection CBD – enhanced anti-inflammatory effect
α-Pinene	Pine trees Rosemary Dill Sage Eucalyptus	Anti-inflammatory Bronchodilator Lessens THC-induced memory loss Increased focus Anti-bacterial Increases permeability of blood-brain barrier	Pine trees “Skunky”	CBD – enhanced anti-inflammatory effect THC – enhanced bronchodilatory effects
Humulene *isomer of β-Caryophyllene	Hops Basil Coriander	Anti-inflammatory Anti-cancer Anti-bacterial Suppresses appetite	Herbaceous Earthy	

Linalool *precursor ingredient in formation of Vitamin E	Lavender Citrus Birch Coriander Rosewood	Anti-anxiety Analgesic Anti-convulsant Sedating, calming Active against acne bacteria Anti-cancer	Floral Spicy Citrus	CBD – enhanced anti-anxiety and analgesic effect THC – enhanced sedation and analgesic effect CBD/THCV/CBDV – enhanced anti-convulsant effect
β-Myrcene *most common terpenoid found in cannabis *not found in hemp	Mango Hops Bay leaves Lemongrass Eucalyptus	Sedating Muscle relaxant Analgesic Anti-oxidant Anti-cancer Anti-inflammatory Anti-depressant Anti-bacterial	Cloves Earthy Fruity	THC – may enhance effects of THC CBD – enhanced anti-inflammatory effects CBG – enhanced anti-inflammatory effects
Terpineol	Citrus Cranberry Currants Grapes	Sedating	Lilac (“flowery”) Orange	
Geraniol	Roses Geraniums Lemons	Anti-oxidant Anti-cancer	Roses	
Terpineol *often found in chemovars high in pinene	Mugwort	Anti-anxiety Anti-bacterial Anti-viral Sedating Anti-oxidant	Floral Lilac Citrus	
Cineole	Tea Tree Eucalyptus	Anti-depressant Anti-inflammatory Anti-bacterial Stimulating due to increased cerebral blood flow	Minty Camphor	
Citronellol	Roses	Anti-inflammatory Sedating Anti-cancer		
Borneol	Camphor Wormwood Cinnamon	Analgesic Sedating Bronchodilator Anti-bacterial	Camphor	

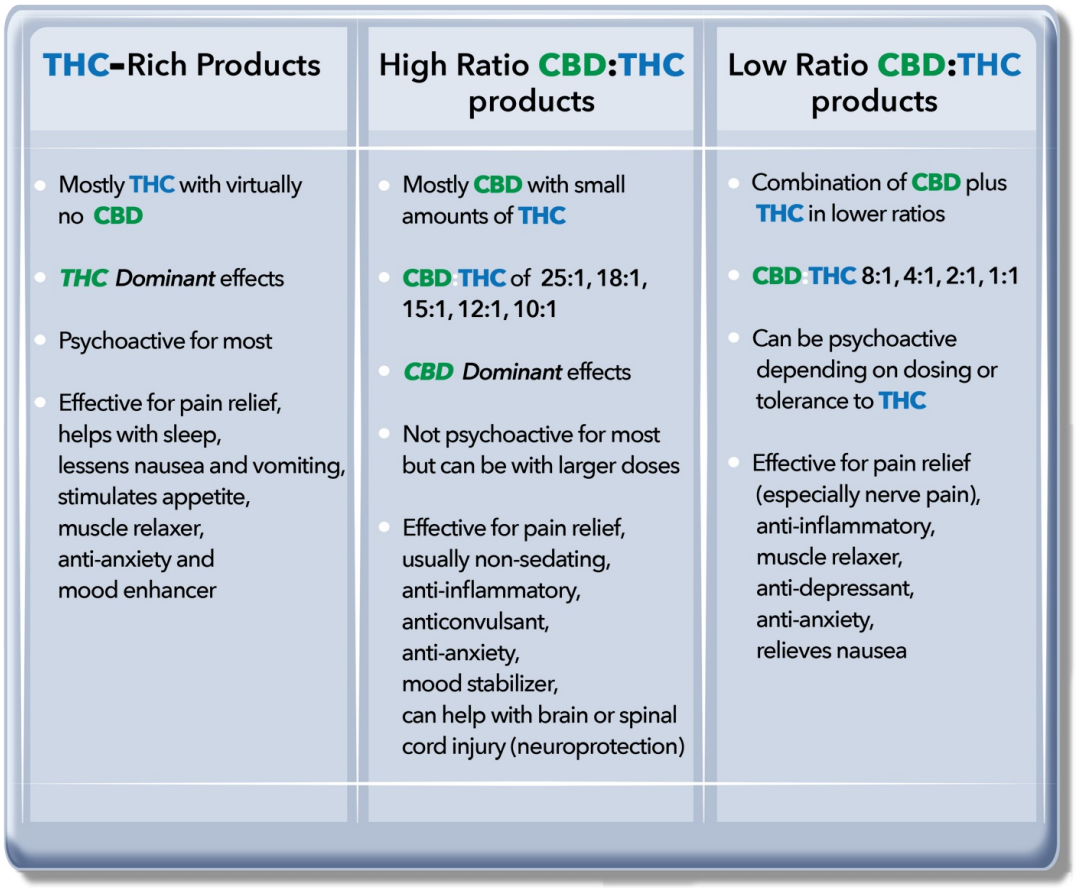
Nerolidol	Citrus rinds Ginger Jasmine	Sedating Anti-fungal	Fruity Woody	THC/CBN – enhanced sedation
Phytol *breakdown product of chlorophyll	Green Tea	Sedating Immuno-suppressant Anti-fungal	Floral Balsamic	
Ocimene	Basil Thyme Alfafa	Anti-fungal Anti-bacterial Decongestant	Thyme Clove Citrus Woody	
Terpinolene *higher in *sativa* chemovars	Conifer trees Nectarines Mangoes Coriander Apples	Sedating Analgesic Gastrointestinal Relief Anti-fungal	Piney Earthy Woody	
Valencene	Oranges	Antiallergy	Citrus Spicy	

Appendix F: Cannabis Dosing Guidelines for Adults

Effects of THC	Effects of CBD
• Psychoactive – "high" • Sedating/relaxing • Reduces pain • Relaxes muscle spasms • Stops nausea/vomiting • Stimulates appetite • Induces sleep • Reduces anxiety & depression • Anti-tumoral effects	• NOT psychoactive – no "high" • Alerting in low doses and sedating in high doses • Reduces pain • Relaxes muscle spasms • Potent anti-inflammatory • Stops nausea/vomiting • Reduces anxiety and depression • Stops psychotic thoughts • Anti-oxidant • Anti-convulsant • Neuro-protectant • Anti-tumoral effects

Where to start

- There is no "one size fits all" with cannabis medicine! The same chemovar or product can give different people different effects. You must be willing to try different products to find what is effective for your condition.
- Most patients who are unfamiliar with cannabis medicine often start with products that have higher amounts of CBD (higher CBD:THC ratios) and depending on results, may then try products that contain increased amounts of THC (low ratio CBD:THC).
- Many patients find that products containing higher amounts of THC are more effective for sleep.



Dosing Guidelines

- First decide how you want to take your cannabis medicine. Options include vaporizing, ingestion, topical, and sublingual methods. Each of these has advantages and disadvantages and you may need to try different methods to find what will work for your condition.
- Decide if you want THC-rich medicine, CBD-rich medicine or a combination of the two types of cannabinoids. You can calculate the CBD:THC ratio by dividing the total CBD in the product by the THC in the product. DO NOT USE UNTESTED MEDICATION! Use the chart to determine what the most likely effects of a product will be.
- Start with a low dose especially if you are new or inexperienced with using cannabis medicine. After taking a small amount, wait at least one hour for the effects. Take another small dose if you did not get the desired effect. This is called "titrating up" the dose and this method will help you find the dose that will work for you and will minimize the risk of taking too much.
- If you are not finding benefits, you may need to adjust the dose, ratio or method of use.
- Once you figure out the dose that is effective for your symptoms, use

this dose for a few days to see how you feel. After a few days, adjust up or down on the dose in small increments or try a different product if you are not satisfied with your results.

- Take note of any side effects so that you can discuss these with your doctor.
- It is often helpful to keep a log of products, doses amounts and timing so that you can understand what is working best for your symptoms.

Patient Precautions

- Treat your cannabis medicine the same way you treat your other medication. This medicine may have different effects on others so do not share your medicine with family members, friends or children. Use your medicine as recommended by your doctor.
- Don't overuse your cannabis medicine. Follow your doctor's instructions and listen to the advice you received at the dispensary. Remember that "less is more" when using cannabis medicine.
- Keep cannabis medicine away from children and pets. Edibles may look appealing to children and animals, so make sure to avoid any accidental ingestion by keeping your medicine in a safe and secure location.
- Do not drive or operate heavy machinery under the influence of cannabis medicine. If you are using the non-psychoactive form of cannabis (CBD-rich products), try it first at home before you drive or operate heavy machinery to make sure that you do not have limited ability. Wait a number of hours to see how long the medicine lasts in your system so you are aware of the duration of the medicine.
- It is recommended that you do not use alcohol at the same time that you take your cannabis medicines. The combination of cannabis with alcohol may lead to dizziness, increased risk of injury, poor judgment and excessive impairment.

Dosing Methods:

Inhalation	Ingestion
• Onset in minutes • Peak effect in 30 minutes • Lasts 1-4 hours depending on dose • Easier to dose since effects are felt immediately • Vaporization is highly recommended over smoking	• Onset in 90 minutes • Peak effect in 2-3 hours • Lasts 6-8 hours • Difficult to dose – start with small amount and titrate up as needed • THC is changed to a stronger compound when eaten; be aware that a small amount can be potent
Sublingual	**Topical**
• Onset in 15-60 minutes • Peak effect in 1-2 hours • Lasts 1-4 hours • Available as drops or sprays • Place under the tongue	• For external skin use only • Does not cause any psychoactive ("high") effects • Apply to bony joints, such as hands, feet, knees, etc. • May also be used on rashes, such as eczema and psoriasis

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You can find more information and links to articles and other sources on the website:

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