



CYTOGEN™

Pain & CBD

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A white paper about the pain that plagues far too many, the detrimental effects of current treatments, and how CBD is delivering hope.

Contents

Introduction	3
What is CBD?	4
The Science Behind CBD: How it Works for Pain and Pain-Related Symptoms	5
Body Chemistry Matters	6
CBD'S Benefits	7
CBD and the Opioid Epidemic	9
Conclusion: CBD is Just Getting Started	10
FAQ:	11
References	15

Introduction

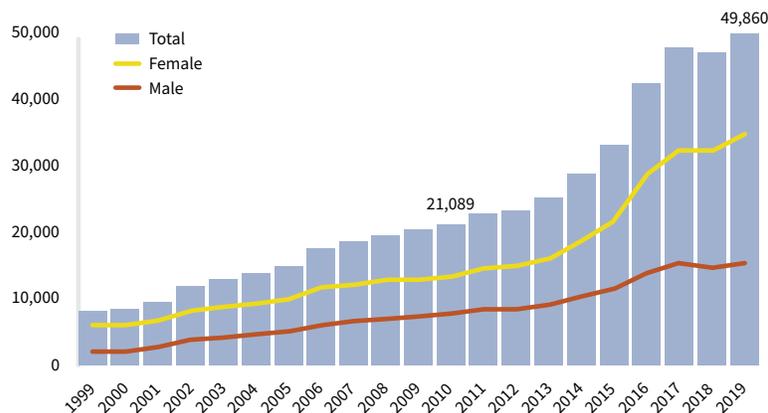
If you're not directly impacted by chronic pain, chances are you know someone who is. Simply typing "Pain in America" into a Google search bar returns 996,000,000 results. Pain is a universal experience. Common chronic pain conditions affect nearly 100 million U.S. adults at the cost of \$560-635 billion annually in direct medical treatment costs and lost productivity.¹ Pain's occurrence, severity, duration, response to intervention, and disabling consequences vary from person to person because pain, like other severe chronic conditions, is much

more than a biological expression and has powerful emotional and cognitive effects. Pain can be mild; it can be acute and recede with treatment; it can be recurrent over months or years; it can be chronic and debilitating, requiring almost constant attention and accommodation.

Opioids, one of the leading pain treatment modalities, have driven an epidemic in America responsible for more than 841,000 deaths since 1999 from an overdose, and that number is on the rise. Over 70% of drug

overdose deaths in 2019 involved an opioid.² Western medicine presents limited sustainable options for pain (noted danger above) as petroleum-based pharmaceutical drugs only target symptoms but does not treat pain's root cause. The advent and isolation of Cannabidiol (CBD) as a grassroots therapeutic option has changed the national conversation about pain. It is no longer a question of whether CBD works—today, the key question is how to use CBD for maximum therapeutic benefit.

Figure 3. National Drug Overdose Deaths Involving ANY Opioid, Number Among All Ages, By Gender, 1999-2018



* Among deaths with drug overdose as the underlying cause, the any opioid subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Center for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

Sir John Russel Reynolds, neurologist, epilepsy research pioneer, and a physician to Queen Victoria back in 1859, asserted,

“For the relief of certain kinds of pain, I believe, there is no more useful medicine than Cannabis within our reach.”⁶



Cannabis was used for pain relief in all major ancient civilizations from Asia through the Middle East and into Europe and the Americas. The scientific inquiry into cannabis has confirmed that it is an effective and safe analgesic for many kinds of pain over the past several decades.

What is CBD?

Cannabidiol or CBD is a non-intoxicating component of the cannabis plant with enormous therapeutic potential. Although CBD does not make people feel high like THC does, it has caused quite a buzz among scientists, health professionals, and medical marijuana patients.

They have been using CBD-rich products to treat a wide range of conditions—chronic pain, cancer, Crohn’s, diabetes, rheumatoid arthritis, PTSD, cardiovascular disease, anxiety, antibiotic-resistant infections, multiple sclerosis, schizophrenia, and more.

Academic research centers in the United States and elsewhere are currently studying the effects of CBD on these and other ailments. Scientists refer to CBD as a

“promiscuous” compound because it confers therapeutic benefits in many different ways while tapping into how we function physiologically and biologically on a deep level.

Research shows that 62% of people who use CBD for a medical condition are treating chronic pain, arthritis, joint pain, and anxiety.³



The World Health Organization describes Cannabidiol as follows:

“In humans, CBD exhibits no effects indicative of any abuse or dependence

potential . . . To date, there is no evidence of public health-related problems associated with the use of pure CBD.”



The World Anti-Doping Agency (WADA) removed hemp-derived Cannabidiol (CBD) from its 2018 List of Prohibited Substances, freeing up athletes in the largest international athletic associations in the world like the IOC and FIFA as well as major sports leagues like UFC, NCAA, NFL, NBA, NHL, MLB, and many more to use CBD-infused products as to treat pain and inflammation-based disorders.



The Science Behind CBD: How it Works for Pain and Pain-Related Symptoms Our Natural Endocannabinoid System

Our body's endocannabinoid system (ECS) is composed of three main components:

1. Cannabinoid receptors, namely CB1 and CB2. CB1 receptors are predominantly found in the central nervous system (CNS, the nerves attached along the spinal cord and around the brain) and are primarily responsible for the cognitive and emotional effects of cannabis, as well as our perception of pain. CB2 receptors are more common in our peripheral nervous system (PNS, the outer nerves beyond the spinal cord and brain such

as those in your arms and legs, although these receptors may also be found in our CNS), and immune cells.

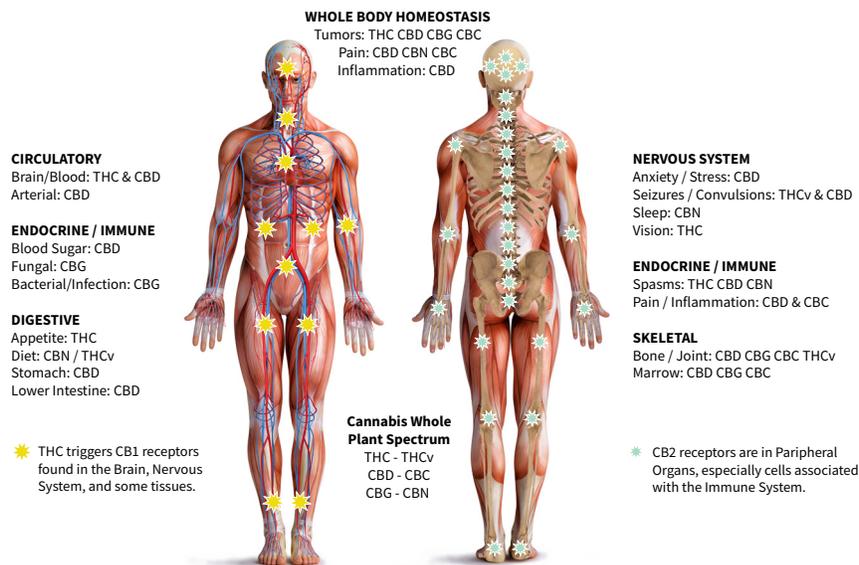
2. Endogenous cannabinoids (the cannabinoids that our bodies produce)
3. Enzymes that facilitate the breakdown and use of cannabinoids

Our natural endocannabinoids synthesize on-demand, meaning that when the body senses inflammation or needs to return to homeostasis (a state of stable balance), it will release endocannabinoids that bind to cannabinoid receptors.

However, CBD itself does not bind to receptors but is thought to work by inducing other components of the cannabinoid system.

CBD exerts a myriad of effects on the body's central and peripheral nervous systems, as well as the immune system. It works in harmony with the endocannabinoid system to function in an antioxidant capacity, decrease systemic inflammation, and act as an analgesic or pain reliever. CBD may even slow the progression of osteoarthritis and prevent nerve damage, according to early model studies.⁵

THE ENDOCANNABINOID SYSTEM



The Human Endocannabinoid System is comprised of two types of receptors: CB1 and CB2, which serve distinct functions in human health and wellness. In addition to certain Terpenes may also aid in effectiveness and impact.

Body Chemistry Matters

The way the endocannabinoid system works, the bioavailability of CBD is an essential factor in how someone will ultimately respond. Bioavailability is the amount of a substance that successfully makes it into the bloodstream and has an effect.

The amount of CBD that an individual absorbs when taking a CBD product works the same way and will depend on:

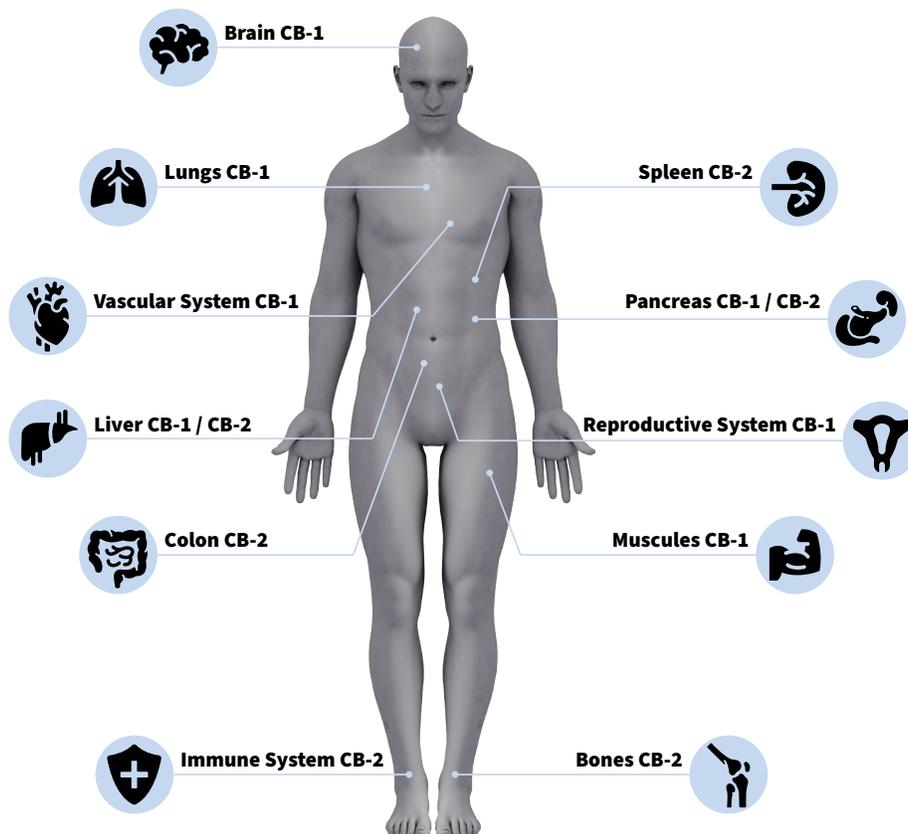
- **Form of administration:** For example, CBD edibles may be better absorbed when taken with food, especially fatty foods. CBD is a lipid-based compound in its natural state and is carried by and absorbed better when

suspended in oil-based elements like hemp or MCT oil.

- **Weight and cannabis experience:** CBD may be taken according to weight like any medication or supplement. However, two people of the same gender and weight may respond very differently to the exact dosage due to factors such as metabolism, body composition, epigenetic expression, and history of using cannabis products.
- **Epigenetic Expression:** Lifestyle and environmental factors can exert long-term effects on gene expression

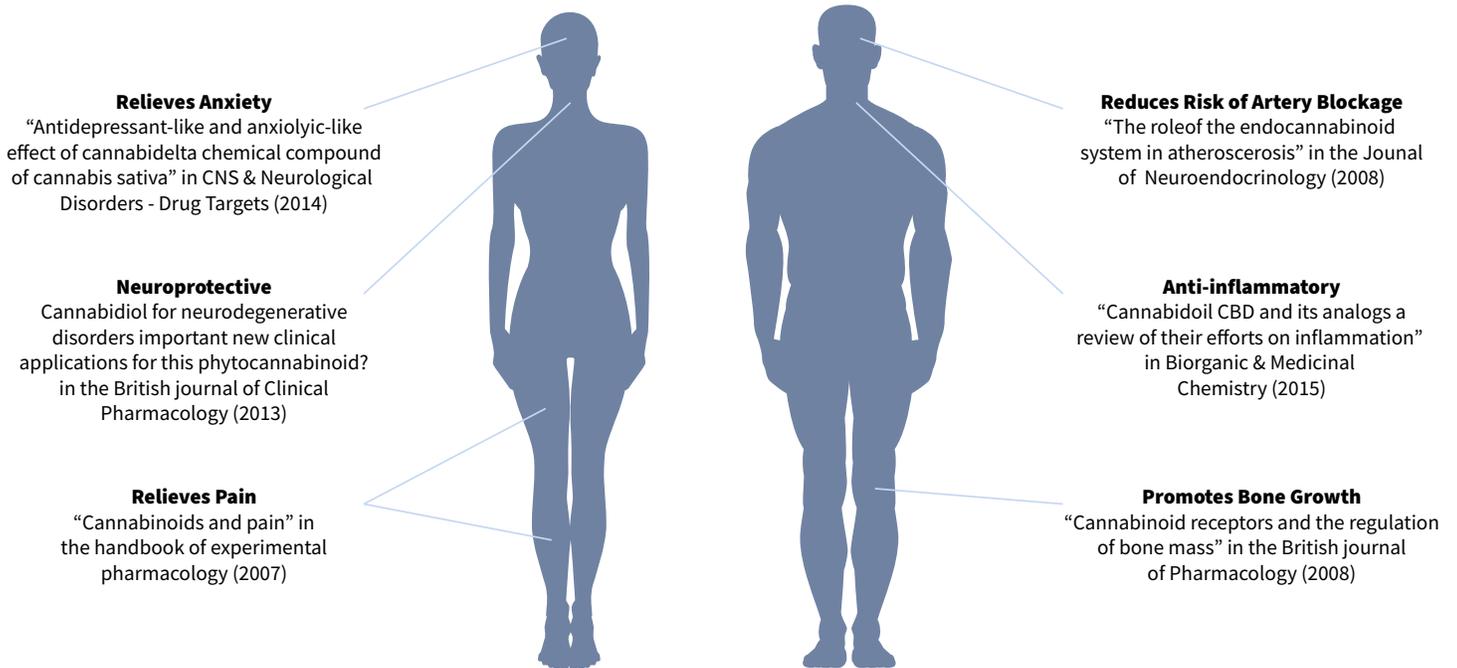
without any change in the nucleotide sequence of DNA, affecting health maintenance and influencing both disease load and resistance. Nutritional status, diet, alcohol abuse, physical activity, stress, and exposure to pollutants, pesticides, or endocrine disruptors, among other aspects, can epigenetically affect gene expression.

- **Daily habits:** Whether an individual has eaten, slept, or manage daily stress habits, it can all affect how the body responds to taking CBD. Inflammatory responses from SAD (Standard American Diet) are a major contributing factor to the pain epidemic in the U.S. today.



CBD'S Benefits

HOW CBD WORKS IN THE HUMAN BODY



Notably, CBD is hydrophobic and lipophilic, meaning it will dissolve in fats. The dissolution helps it to be carried across the blood-brain barrier and affect the CNS, where it can have a broad range of positive effects on pain, including:

- **Reducing Pain Signals**
 - CBD modulates pain and the sensation of pain by stimulating the reuptake of the neurotransmitter adenosine, thereby boosting adenosine levels in the brain and inhibiting pain sensations. CBD may also block pain signals from reaching processing centers in the brain by binding to TRPV1, which

is responsible for pain and inflammation.⁷⁻⁹

- **Increasing Immune Response** – CBD can modulate the immune response by decreasing levels of pro-inflammatory cytokines and inhibits the proliferation of T-cells that are indicated in autoimmune and systemic inflammatory disorders.¹⁰
- **Reducing Inflammation** – CBD decreases oxidative stress and systemic inflammation by acting as an antioxidant. CBD may also decrease inflammation by preventing a reduction in

microelements like zinc and selenium, which are essential elements for a balanced immune response, and may reduce neuropathic pain (such as fibromyalgia or neuropathic pain) by countering hyperalgesia (an abnormally heightened pain response).

- **Improving Mood and Sleep**
 - Chronic pain can disrupt daily life, relationships, work, emotional and mental health. If facing anxiety, depression, insomnia, and fatigue – all typical with chronic pain – CBD may help relax or provoke the restful needed.

Pain White Paper

Given these benefits, CBD is thought to help ease the symptoms of the following conditions (partial list):

- **Osteoarthritis** – this painful joint condition has been examined quite a bit in relation to CBD. Some early studies show that CBD acts as an antagonist and blocks or debilitates the GPR55 receptor, which may slow osteoarthritis by facilitating bone reabsorption.⁵
- **Type 2 Diabetes** – CBD activates a receptor called PPAR-gamma, which may increase insulin sensitivity, an essential step in improving type 2 diabetes and decreasing the risk for developing diabetes-related neuropathic pain.¹¹
- **Cancer and Alzheimer’s** – CBD may exert an anti-cancer effect via the debilitation of GPR55 receptors in the body and by activating the PPAR-gamma receptor, which also degrades amyloid-beta plaque, a key molecule linked to the development of Alzheimer’s disease.¹¹
- **Lupus and Rheumatoid Arthritis** – CBD continues to be studied for these inflammatory and autoimmune conditions, as well as for fibromyalgia. Here is more on cannabinoids and lupus.
- **Multiple Sclerosis** – there are mixed data for the use of CBD (as well as THC) in helping to reduce MS-related pain and spasticity.¹²
- **Anxiety** – as noted, anxiety related to living with chronic pain, or that exists on its own, maybe eased with CBD use, whether temporarily or in the long term.

Cannabinoids affect the transmission of pain signals from the affected region to the brain (ascending) and from the brain to the affected region (descending). A 2011 study showed that CBD and CBC (another identified cannabinoid found in cannabis) stimulated descending pain-mitigating pathways in the nervous system and caused analgesia by interacting with several target proteins involved in nociceptive control.

Authors concluded that the cannabinoids “might represent helpful therapeutic agents with multiple mechanisms of action.”¹³

The following year, researchers reported that CBD significantly suppressed chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in animals.¹⁴ And then, in 2013, researchers concluded that chronic pain patients prescribed hydrocodone were less likely to take the painkiller if they used cannabis.¹⁵

Be mindful that while Cannabidiol has many benefits, it is not a silver bullet and should not be viewed as an alternative to other pain treatments. CBD should be considered a complementary modality to add to pain management resources.

Studies show that CBD oil helps with:

- + General Well-Being
- + Acne
- + ADD / ADHD
- + Addiction
- + AIDS
- + ALS
- + Alzheimer’s
- + Anorexia
- + Antibiotic Resistance
- + Anxiety
- + Asthma
- + Atherosclerosis
- + Arthritis
- + Autism
- + Bipolar
- + Cancer
- + Colitis / Chrons
- + Depression
- + Diabetes
- + Endocrine Disorder
- + Epilepsy / Seizure
- + Fibromyalgia
- + Glaucoma
- + Heart Disease
- + Huntington’s
- + Inflammation
- + Irritable Bowel
- + Kidney Disease
- + Mad Cow Disease / Prion
- + Metabolic Syndrome
- + Migraine
- + Mood Disorder
- + Motion Sickness
- + Multiple Sclerosis
- + Nausea
- + Neuropathic Pain
- + Obesity
- + OCD
- + Osteoporosis
- + Parkinsons
- + PTSD
- + Rheumatism
- + Skin Conditions
- + Sleep Disorders
- + Spinal Cord Injury
- + Stress
- + Stroke / TBI

CBD and the Opioid Epidemic



CBD and other cannabis-based medicines have the potential to be a powerful tool in the war against the current epidemic of pharmaceutical drug abuse and overdose in the United States. They have been used successfully as a substitute for opioid-based medicines for pain relief, allowing people to lower their dosages and prevent addiction.

Reduced Opiate Use

Cannabis and narcotic painkillers are known as co-agonists, which means that each of them magnifies the effect of the other. This allows patients to take lower doses with comparable effectiveness. One recent study of 300 people using high doses of opioids to control pain found they could reduce their opioid intake by 60% within three weeks of taking CBD and still manage their pain at the same level. After two months, many of them were able to get off the opioid medicine altogether.¹⁶

Decreased Withdrawals

CBD has also been used successfully to ease symptoms from opiate withdrawal during the addiction recovery process. It also decreases the physical craving for opiates. It has been said in the past that cannabis is a gateway drug. In reality, it is a gateway in the other direction, a

gateway out of addiction. It is a drug that is used to facilitate the healing of people addicted to hard drugs. As reported in 2015, the sales of pharmaceutical opioid drugs have dropped by 5% in states that have legalized cannabis.¹⁷

In the June of 2016, an issue of The Journal of Pain, researchers Boehnke, Litinis, and Clauw showed that medical cannabis use was associated with a 64% decrease in opioid use in patients with chronic pain. In addition, there was a decrease in the number and side effects of medications and an average of 45% improvement in quality of life measures – benefits greater than other classes of medications and with fewer side effects.¹⁸

Opioid-Sparing

CBD Oil can be used as an adjunct medication for opioid-sparing. Opioid-sparing means using another less hazardous medication to decrease or spare the number of dangerous opioids used. Currently, physicians use anti-inflammatory medications, antidepressants, anticonvulsants, and topical analgesic preparations, to reduce the number of opioids necessary for adequate pain control. Opioid sparing implies that a lesser dose of opioid can be used to get the same effect through synergistic effects of non-

opioid medications. CBD also has a positive impact on mood, anxiety, commonly associated with chronic pain syndromes. Also, CBD positively impacts inflammation and spasm, which often accompany chronic pain.

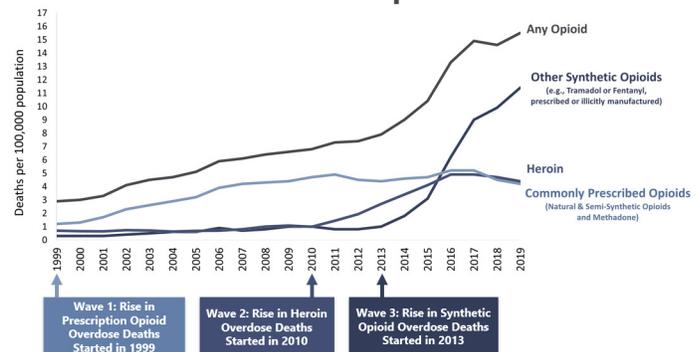
Fewer Overdoses

Decreasing opioids via opioid-sparing leads to fewer accidental overdoses and fewer adverse events such as severe constipation. A recently released analysis of the literature from the National Cannabis Industry Association (NCIA) discussed some promising observational and population-based findings supporting the use of CBD and medical cannabis as an adjunct to opioids and for tapering off opioids.¹⁹

CBD Is Not a Culprit

Unfortunately, opioid receptors are heavily expressed on the respiratory centers in the brainstem. Therefore, high doses of opioids can cause respiratory depression, the most common cause of opioid overdose death. There are essentially no cannabinoid receptors in the brainstem, which is the primary reason that no overdose deaths have ever been associated with cannabis use.

Three Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

Conclusion: CBD is Just Getting Started

Who would have thought a plant that remains in a Schedule 1 category with no medicinal value along with heroin, would actually be a countermeasure necessary for bringing people out of opiate

addiction? Physicians and other health professionals are working with CBD in the United States and around the world, but the industry remains in the embryonic stages relative to its potential. With continued education

and training, cannabinoids like CBD will continue to become common practice as safe and efficacious ways to fight and prevent disease naturally.



FAQ:

Which cannabinoid is better for pain, THC or CBD?

There is no definitive answer to the debate between THC and CBD for pain relief. Cannabis is still considered a Schedule 1 drug by the federal government — a legal status limiting the kinds of research that can be conducted. Cannabis should immediately be moved to a less restrictive Schedule considering its safety and comprehensive medicinal profile.

Utilizing the available current research, a

combination of THC and CBD together shows the most promise for pain relief.

These cannabinoids provoke a powerful synergy, essentially potentiating the health benefits of each of the cannabinoids.

A recent study in Neurology found THC is effective for alleviating chronic nerve pain. A more extensive study involving 177 cancer patients found that while THC was not effective at reducing pain, the patients who took a CBD/THC combination had their pain reduced by over 30 percent compared to placebo. Another

double-blind study supported this conclusion when using THC for post-surgery pain. Meanwhile, a 2017 study found that both THC and CBD, when taken alone, were effective for reducing chemotherapy-related pain in mice.

The same study also discovered that previously ineffective CBD and THC doses could relieve pain when combined. This relates to an important benefit of THC – it can enhance the pain-relieving properties of CBD through what is known as the entourage effect.

CC1=C(C(=C(C=C1)O)C2=CC(=C(C=C2)O)C3=CC(=C(C=C3)C)C)C

CBD

VS

CC1=C(C(=C(C=C1)O)C2=CC(=C(C=C2)O)C3=CC(=C(C=C3)C)C)C

THC

 Non-psychoactive	 Neuroprotectant	 Anti-convulsant	 Antioxidant
 Anti-inflammatory	 Anti-tumoral	 Anxiolytic	 Assists Homeostasis

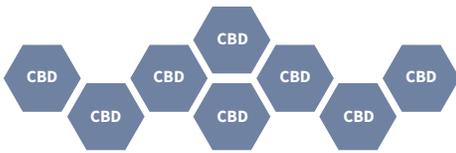
 Psychotropic	 Anti-nausea	 Anti-cancerous	 Glaucoma Relief
 Analgesic	 Neuroprotectant	 Appetite stimulant	 Anti-inflammatory

What are the primary categories of CBD and which is the best for me?

Cannabidiol can be used separately from all other cannabinoids; this is considered isolated CBD. CBD can also be used in combination with other valuable cannabinoids, such as CBG, CBN, CBC, and THC. This is known as full-spectrum CBD or broad-spectrum CBD.

ISO-CANNABINOID

(Isolated CBD only)



Isolated CBD:

The isolated CBD is self-explanatory; Isolate refers to the isolated CBD molecule in its pure and isolated form. CBD Isolate can be extracted and processed from two sources: the industrial hemp plant or the entire cannabis plant, also known as marijuana, for those who prefer slang. Considering the molecular extraction of pure CBD, there is no difference in the CBD extracted from hemp or the CBD extracted from the whole plant cannabis.

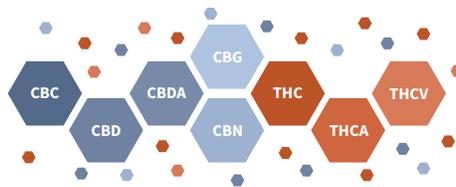
Best For:

- Individuals who were recommended to take high doses of CBD specifically
- Individuals with sensitivity to THC or other cannabinoids
- Individuals who regularly undergo drug screening tests
- Individuals who prefer light flavors or no flavor
- Individuals living in states that have strict THC-laws

- First-time users that may be hesitant about other cannabinoids

FULL-SPECTRUM

(Everything from source plant)



Full-Spectrum CBD:

Full-spectrum CBD is accompanied by other cannabinoids, flavonoids, terpenoids, chlorophyll, and other phyto-botanical constituents of hemp, including THC. It is imperative to note that the main difference between Isolate, Full-Spectrum, and Broad-Spectrum products is the presence of THC (tetrahydrocannabinol). THC is the famous cannabinoid that causes a user to feel “high” or “high” after smoking or ingesting.

Best For:

- Individuals who were recommended a particular THC:CBD ratio
- Individuals with more severe conditions or conditions that CBD isolate and Broad-Spectrum could not alleviate
- Individuals living in states where Cannabis is legal

from full-spectrum CBD oil in that it contains zero THC. However, it contains all other cannabinoids, terpenoids, flavonoids, and other botanical elements. When all of these phytoactive ingredients are taken together, they work together to produce a stronger therapeutic effect.

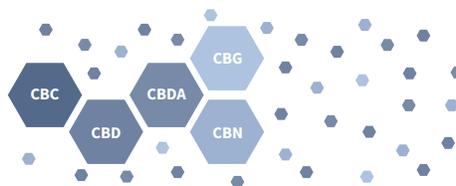
Broad-spectrum CBD provides a variety of cannabinoids working in sync with CBD (minus THC), offering a more versatile product without the responsibility of doing a positive drug test.

Best For:

- Individuals with conditions that CBD isolate alone could not alleviate
- Individuals with sensitivity to THC
- Individuals living in states that have strict THC-laws
- First-time users that are hesitant about THC

BROAD-SPECTRUM

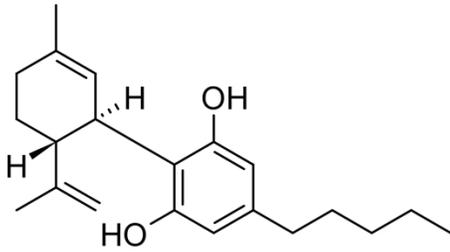
(Everything except THC)



Broad-Spectrum CBD:

Broad-spectrum CBD oil differs

Pain White Paper



What is a general therapeutic dose of CBD for chronic pain?

It is suggested that patients work with a healthcare practitioner experienced in recommending CBD or medical cannabis to develop and tailor dosage and delivery methods on an individual basis.

Finding the correct dose of CBD for a particular patient is not an easy task, even for experts, because there are so many different factors that play an essential part in the patient's experience:

- The medical condition or problem
- The condition's stage or intensity
- The patient's biology and metabolism and how they respond to CBD
- The patient's endocannabinoid system and how it functions and acclimates to CBD over time
- The patient's body weight
- The patient's sensitivity to cannabis – this is critical
- The patient's body chemistry, including pharmaceuticals and foods ingested

Standard doses are mid-range, between 10mg and 100mg of CBD/ daily.

Are there commercial medications that can have a negative interaction with CBD and other cannabinoids?

CBD has very few known adverse side effects at any dose. According to research, high doses of up to 1500mg/daily of CBD seem to be well tolerated in humans.²⁰ THC in high doses can make a person feel out of sorts for a while, but there are no known fatalities from overdosing on cannabis, as there are for many pharmaceutical drugs.

CBD and other plant cannabinoids can potentially interact with many pharmaceuticals, decreasing their effectiveness by inhibiting the activity of cytochrome P450, a family of liver enzymes. This potentially affects the body's metabolism of a wide range of compounds – up to 60% of commonly prescribed pharmaceuticals. The primary issue is that CBD is metabolized by cytochrome P450 enzymes, occupying the site of enzymatic activity and preventing it from metabolizing other compounds.

Research has suggested that CBD can amplify the activity of specific cytochrome P450 enzymes. This evidence suggests that CBD can either increase or decrease the breakdown of other drugs, depending on the medication in question and the dosages used.²¹

A partial list of drugs that use the cytochrome P450 system include²²:

- Steroids
- HMG CoA reductase inhibitors
- Calcium channel blockers
- Antihistamines
- Prokinetics
- HIV antivirals
- Immune modulators
- Benzodiazepines
- Anti-arrhythmic
- Antibiotics
- Anesthetics

- Antipsychotics
- Antidepressants
- Beta-blockers
- PPIs
- NSAIDs
- Angiotension II blockers

When taking CBD and any of these drugs, it is essential to establish a dosing strategy that allows each drug



and CBD compound to metabolize independently. If both are taken together at the same time, only one will be metabolized. It is imperative to stagger doses and establishes a sound medication management strategy.

Do diet and nutrition play a role in how CBD and other cannabinoids work in the body?

Certain foods can affect CBD bioavailability. In a 2013 study published in the European Journal of Clinical Pharmacology, researchers assessed the effect food had on single-dose bioavailability of a delta-9-tetrahydrocannabinol (THC) and CBD oromucosal spray among twelve healthy men. The study found that bioavailability was around four times higher when the spray was used following a meal than on an empty stomach.

Patients at the MINCEP Epilepsy Care Clinic received a single dose of 99% pure CBD capsules under

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Andrew Serafini

Chief of Education for Global Health Brands

Mr. Serafini is a former firefighter/medic and pioneer in the medical cannabis and CBD industries. Since 2014, Andrew has co-founded and launched several CBD companies and brands focusing on the importance of wide-spread education for patients and medical professionals alike while producing medically-geared CBD and adaptogen-based products for the management of acute and chronic illnesses.

Educating and training physicians/licensed professionals in the US and Brazil on the functional and clinical uses of cannabinoids, Andrew has a unique skillset with deep experience with the business of cannabinoids, but concurrently understanding the medical uses for cannabinoids across a number of disparaging diseases. Holding a Cannabis Science and Medicine Certificate from The Robert Larner, M.D. College

of Medicine, University of Vermont; Professional Certificates from The Medical Cannabis Institute in Clinical Cannabinoid Medicine; a graduate of the Green Flower Media Cannabis Fundamentals Certificate Program; and Foundation of Cannabinoid Medicine Program Certificate from The Advent Academy, Mr. Serafini has alongside many of the brightest researchers and medical practitioners in Integrative and Cannabis Medicine.

Additionally, he has worked with thousands of patients over his tenure in the CBD and medical cannabis industries, and is currently enrolled at the Functional Medicine Coaching Academy in collaboration with the Institute of Functional Medicine.

Serafini serves as the Chief of Education for Global Health Brands, makers of **CYTOGEN**[™] Medicinal Cannabidiol Products approved by ANVISA Health Regulatory Agency, Brazilian Ministry of Health. **CYTOGEN**[™] is written by doctor's prescription for the treatment of ten health conditions in Brazil including epilepsy (Dravet and Lennox Gastaut), Alzheimer's Disease, arthritis, chronic pain, MS, fibromyalgia, Irritable Bowel Disease, Autism Spectrum Disorder, Parkinson's Disease and mental health ailments.

For more from Mr. Serafini click [here](https://cytogenmd.com/about/), <https://cytogenmd.com/about/>