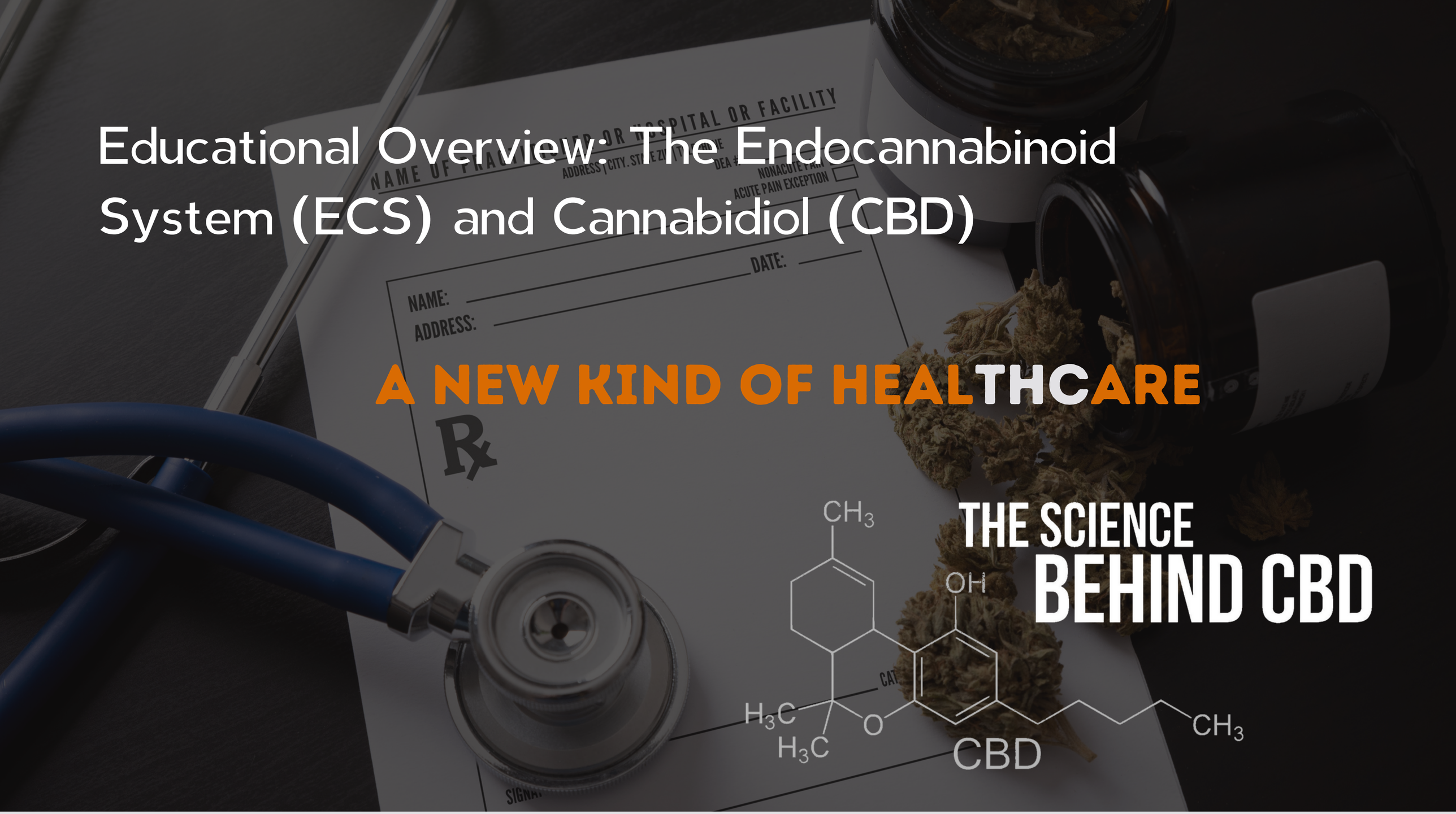
# Educational Overview: The Endocannabinoid System (ECS) and Cannabidiol (CBD)

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# Current Status

- **President Donald Trump** signed **the** 2018 Farm Bill federally legalizing the cultivation and sale of industrial hemp, which is defined as cannabis that contains less than **0.3-percent THC**. Congress passed the $867-illion agricultural legislation, Section 12619 (B) of the Farm Bill **permanently removed industrial hemp** from the Controlled Substances Act; **allowing states to regulate its production, commerce and research with approval from the USDA**. Accordingly, hemp and its derivatives are **no longer considered marijuana** but deemed an **agricultural commodity** and therefore **no longer classified as Schedule 1 controlled substances under the controlled substances(CSA);** the growing and selling of hemp and hemp-derived products through interstate commerce are **now legal**.
- **Since 1996, forty-four states, the District of Columbia, Puerto Rico and Guam** have passed laws that grant their residents the right to possess, cultivate, and/or obtain cannabis (marijuana) or cannabis-based products under the care of their physician to address healthcare needs.
- World Health Organization: CBD Pre-Review Report.
- The World Doping Committee (WADA) removed CBD from banned substances list in 2018.
- USDA says States should not interfere with Hemp Transportation

Today, more than **300 million Americans** live under these laws -- about 85% of the U.S. population. Americans for Safe Access (ASA) has estimated that these medical cannabis programs serve approximately two million patients under physician supervision. Additionally, in part due to **recent legislation on a federal level**, Hemp derived Cannabidiol **(CBD) is readily available** to consumers across the United States and provides an easily accessible entry point into medical cannabis-based therapies, even for patients without a traditional "qualifying diagnosis.

**Some key finding from The World Health Organization (WHO)** *"There are no case reports of abuse or dependence relating to the use of pure CBD."*
*"No public health problems have been associated with CBD use."*
*"CBD has been found to be generally well tolerated with a good safety profile."*
*"There is no evidence that CBD is liable to similar abuse and similar ill-effects as substances…such as cannabis or THC."*
**After a thorough scientific review and analysis, the FDA opined:**
*"There is little indication that CBD has abuse potential or presents a significant risk to the public health."*
*"No evidence for a classic drug withdrawal syndrome for CBD, and no evidence that CBD causes physical or psychic dependence."*
*"CBD does not appear to have abuse potential under the CSA."*
*"There is no signal for the development of substance use disorder in individuals consuming CBD-containing products."*
*"It is unlikely that CBD would act as an immediate precursor to THC for abuse purposes."*

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# Endocannabinoid System (ECS)

**ECS was summarized in 1998 by Professor Di Marzo as, "relax, eat, sleep, forget and protect"**

**Endocannabinoid System (ECS) is a biochemical system** of sophisticated compounds, their receptors, and signaling pathways. The ECS is responsible for **regulating the release of neurotransmitters** resulting in biochemical communication. **The discovery of the endocannabinoid system** has led to the emergence of a **"new physiological system of immense importance"**. world-renowned cannabis expert, **Raphael Mechoulem PhD**.

In 1964, THC was first characterized and synthesized by Mechoulam and Gaoni in Israel. In 1988, the **first cannabinoid receptor was found in a rat brain, CB1. Four years later, a second, CB2, was discovered. CB1 and CB2 receptors** are distributed throughout the CNS, immune system, brain tissue, GI system, reproductive & URInary tracts, endocrine & cardiovascular systems.

In 1992, scientists found the endocannabinoid **anandamide is also known as the "bliss molecule"** are endogenous molecules that, like the native opioids and nicotine like molecules our bodies make, engage the cannabinoid receptors throughout the human body. **The body produces its own cannabinoids** produced internally and plays a major role in maintaining **homeostasis** within the body. **Researchers discovered 2-AG In 1995**. It activates both receptors, CB1 and CB2, unlike anandamide. These endocannabinoids work by interacting with the cannabinoid receptors. They are produced in your cell membranes from fat-like molecules. Your body **synthesizes them on-demand** from an Omega-6 fatty acid, arachidonic acid; as you need them, your body makes and uses them, as opposed to being packaged and stored for use at a later time like numerous other biological molecules.
According to a team of Stony Brook University scientists, **CBD functions as an anandamide reuptake and breakdown inhibitor, thereby raising endocannabinoid levels in the brain's synapses. CBD does not directly stimulate CB1 and CB2,** the canonical **canabinoid** receptors, like THC does.

The **ECS is a very complex regulatory system,** found within all complex animals (not only humans).
**It regulates physiological processes including motor control, mood, memory, appetite, pain, digestion, immune response, neural protection, bone growth, fertility, reproduction, mood & pleasure, temperature regulation and many others.**

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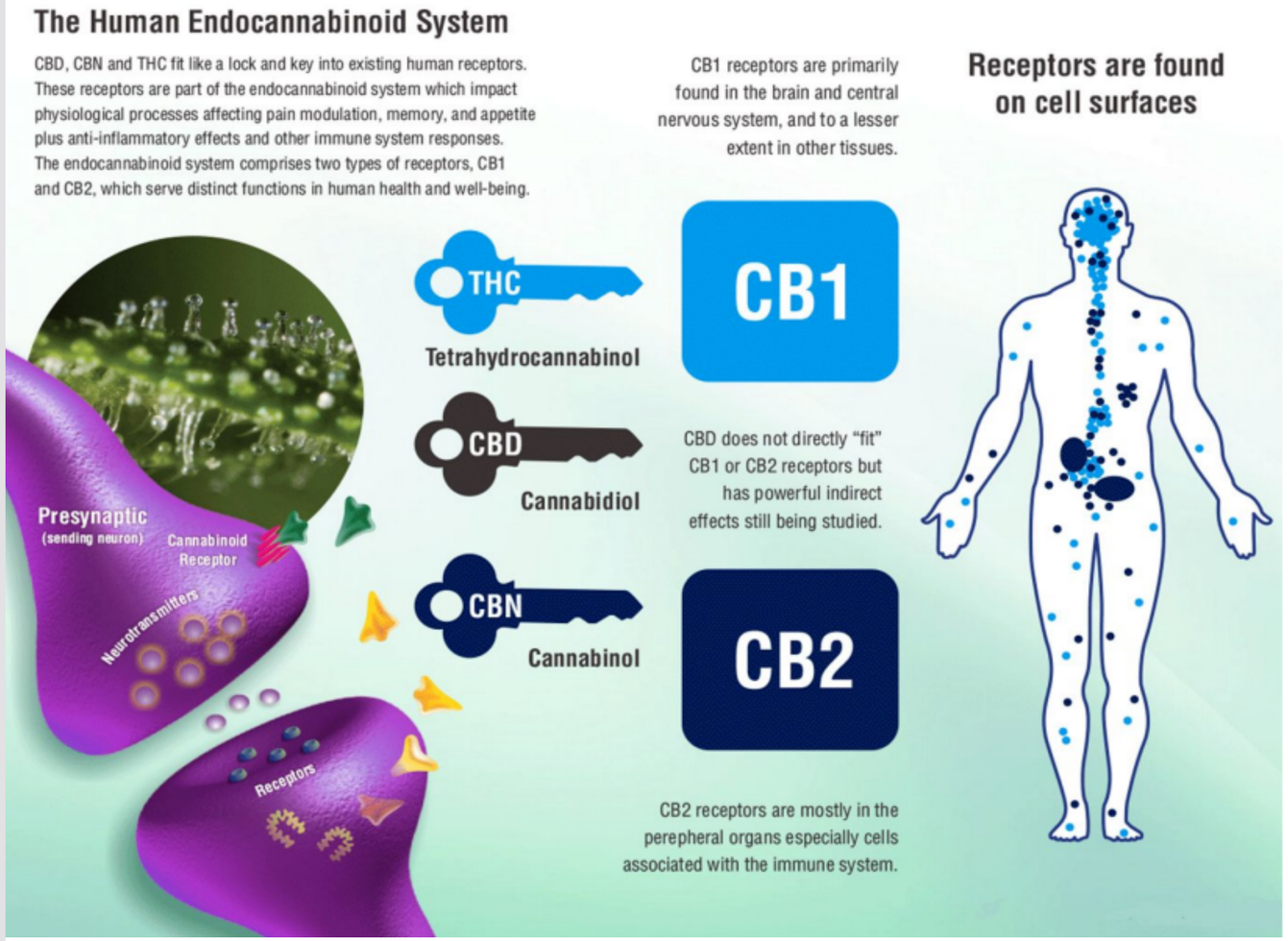
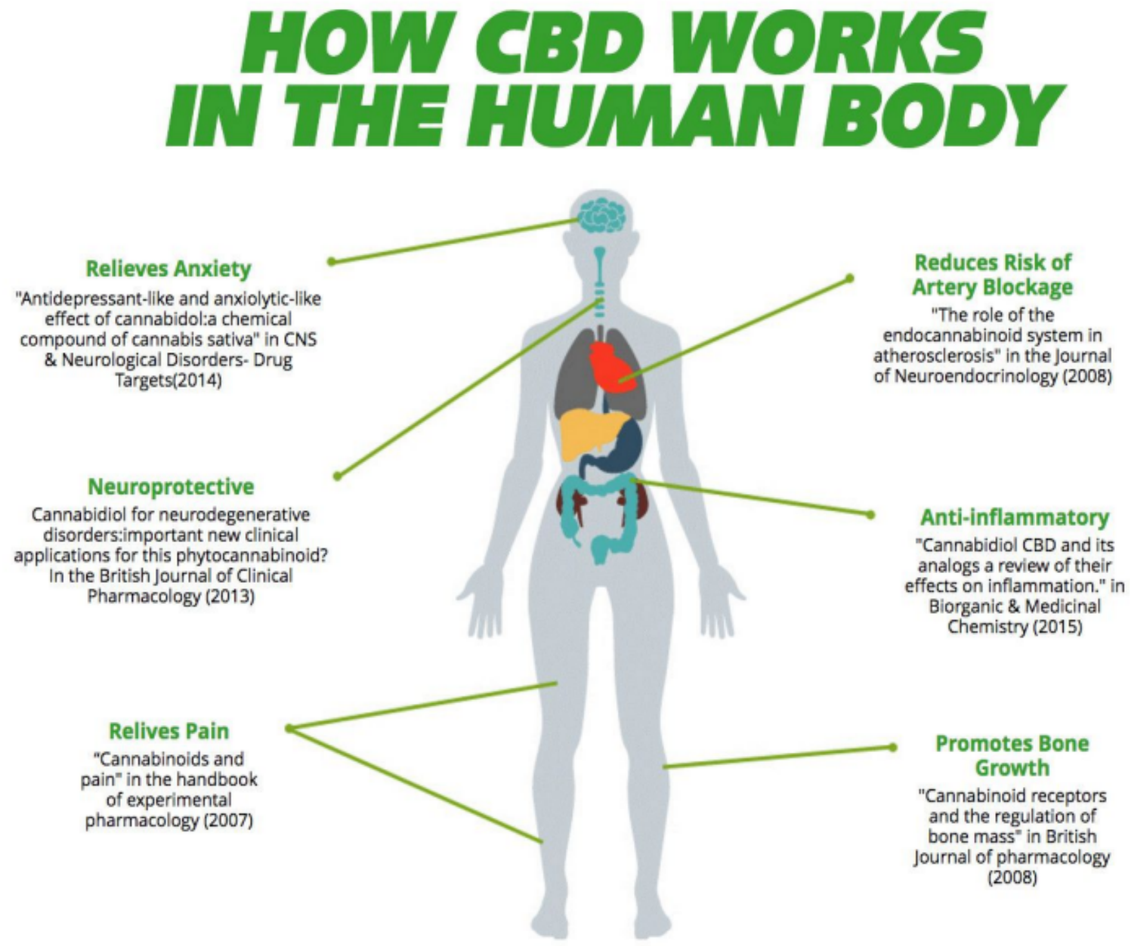
# Endocannabinoid System & Benefits of CBD

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# Terpenes & The Endocannabinoid System

- **Terpenes give cannabis its unique smell, taste, aroma and are the most common plant chemicals in nature.**
- **Terpenes are pharmacologically active and synergistic with cannabinoids.**

**A-PINENE**

ANTI-INFLAMMATORY
BRONCHODILATOR
AIDS MEMORY
ANTI-BACTERIAL

also found in
pine needles

**LINALOOL**

ANESTHETIC
ANTI-CONVULSANT
ANALGESIC
ANTI-ANXIETY

also found in
lavender

**BETA CARYOPHYLLENE**

ANTI-INFLAMMATORY
ANALGESIC
PROTECTS CELLS LINING THE DIGESTIVE TRACT

also found in
black pepper

**MYRCENE**

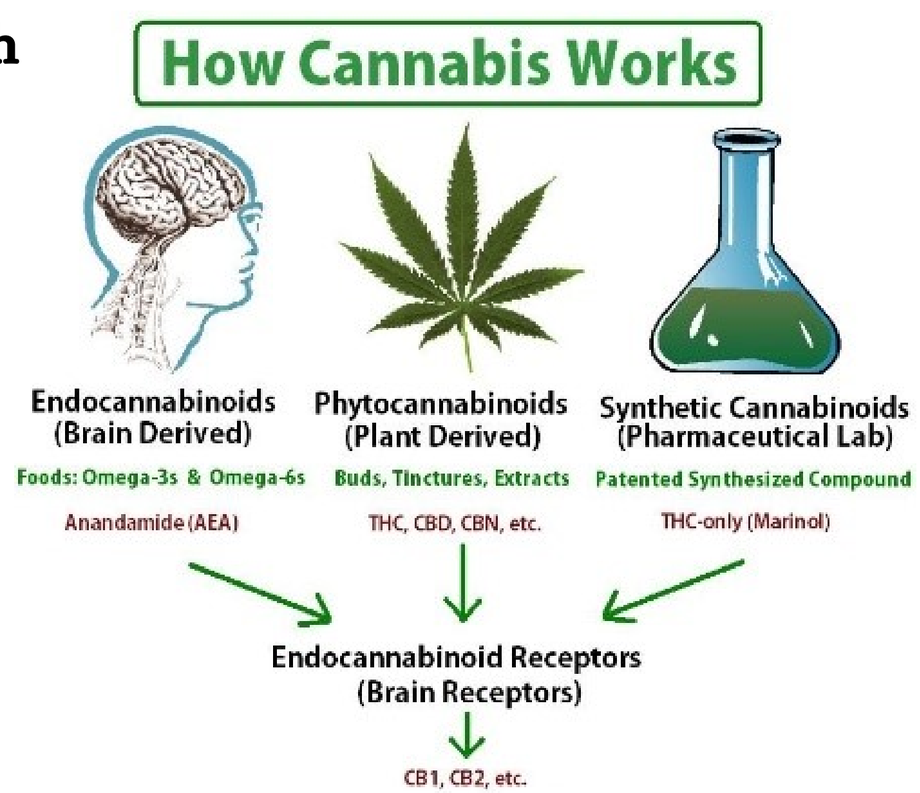
CONTRIBUTES TO SEDATIVE EFFECT OF STRONG INDICAS
SLEEP AID
MUSCLE RELAXANT

also found in
hops

**LIMONENE**

TREATS ACID REFLUX
ANTI-ANXIETY
ANTIDEPRESSANT

also found in
citrus




**The endocannabinoid system (ECS) is involved in regulating a variety of physiological processes including appetite, pain and pleasure sensation, immune system, mood, and memory.**

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# Clinical Endocannabinoid Deficiency

## What if endocannabinoid levels are too low?

It has been theorized that numerous mysterious disorders fit the description of **"clinical endocannabinoid deficiency" (CED**. Noteworthy among these are migraine, fibromyalgia and idiopathic bowel syndrome (IBS or "spastic colon"). **Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency**. These disorders affect millions of healthy people who are plagued by chronic pain and other symptoms. **CED explainned by Dr. Ethan Russo a board certified neurologist**, and medical research director at Phytecs, a biotechnology company that specializes in developing different ways of targeting the endocannabinoid system for therapeutic benefit.

- **The ECS is composed of three principal elements and its purpose is to regulate and balance complex neurochemical signaling throughout the body.**
- **Cannabinoid Receptors (**primarily CB1 and CB2 located on cell surfaces and transmit information about changing conditions**)**
- **Endocannabinoids (**special molecules that activate cannabinoid receptors**)**
- **Enzymes (**synthesize or metabolize endocannabinoids**)**

**Stimulating cannabinoid receptors could help delete traumatic memories** and could **therapeutically benefit age-related disorders linked with brain inflammation Cannabinoids copy endocannabinoid behavior** and have interactions with cannabinoid receptors to improve the ECS. This ideology can help explain the varying efficacy among specific strains/**cannabinoid profiles** and how they work differently on very similar patients.

**As physicians, our experience** with our patients over the years supports **this theory of the ECS being "out of balance" in many disease states** and CBD can be aremedy. **Symptomatic relief has been widely reported** across the board for chronic illnesses that are idiopathic in nature when utilizing cannabinoid therapy.Just like the chemical I'mbalance that is said to underlie a disease such as depression, abnormality in "endocannabinoid tone" can have deleterious consequences to human health. **The significance of the ECS in healthy biological functioning is present without a doubt.**

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# FDA Approved Cannabis Drugs



## 12.1 Mechanism of Action

Dronabinol is an orally active cannabinoid which has complex effects on the CNS, including central sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues. These receptors may play a role in mediating the effects of dronabinol.

## Sativex® (delta-9-tetrahydrocannibinol and cannabidiol in the EU) (nabiximols in the USA)

Sativex® is an oromucosal spray of a formulated extract of the cannabis sativa plant that contains the principal cannabinoids delta-9-tetrahydrocannibinol (THC) and cannabidiol (CBD) in a 1:1 ratio as well as specific minor cannabinoids and other non-cannabinoid components. We developed Sativex® to be administered as an oromucosal spray, whereby the active ingredients are absorbed in the lining of the mouth, either under the tongue or inside the cheek. We have received regulatory approval for Sativex® in numerous countries outside the United States. In Europe, Sativex® has now received marketing authorization in 21 countries for the treatment of spasticity (muscle stiffness/spasm) due to MS.


[FDA Approves First Drug Comprised of an Active Ingredient Derived from Marijuana to Treat Rare, Severe Forms of Epilepsy]

Epidiolex is GW's lead cannabinoid product candidate and is a proprietary oral solution of pure plant-derived cannabidiol, or CBD. GW's Epidiolex development is initially concentrating on severe, orphan, early-onset, treatment-resistant epilepsy syndromes including Dravet syndrome, Lennox-Gastaut syndrome (LGS) and Tuberous Sclerosis Complex (TSC).

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# Cannabinoids & Phytocannabinoids

- **Phytocannabinoids** are **cannabinoids** that occur naturally in the cannabis plant. Over 480 compounds have been found in the cannabis plant, and **at least 85 of theem** include cannabinoids. They exert their effects by interacting with specific cannabinoid receptors present on the surface of cells and have **numerouss neurological benefits**. When the cannabinoids attach to receptors, they activate the receptors and create a physiological response. For example, your brain may receive a message to relax, sleep or eat after cannabinoids interact with cannabinoid receptors in your body.

- **Not all phytocannabinoids attach to receptors**. For example, **CBD does not attach to any receptors**. Instead, **CBD helps** prevent the breakdown of anandamide — the body's natural cannabinoid. Many of the therapeutic benefits of **CBD** are created through indirect actions.
- CBD has a little **binding affinity** for either of the two **cannabinoid** receptors (CB1and CB2), cannabidiol modulates several non-cannabinoid receptors and ion channels. CBD also acts through various **receptor**-independent pathways—for example, by delaying the "reuptake" of endogenous neurotransmitters (such as **anandamide** and adenosine) and by enhancing or inhibiting the binding action of certain G-protein coupled receptors.

- **CBD has contributed** to the development of a synthesized positive allosteric modulator to treat pain and neurological disorders at the University of Aberdeen in Scotland. One of the main ways they impact us is by mimicking and augmenting the effects of our "endogenous cannabinoids".

- **Cannabinoids can be both** psychoactive and/or non-euphoric. Psychoactive cannabinoids, like THC, produce a "high" feeling. CBD, do not get users "high". Both types of cannabinoids offer unique health benefits. P**sychoactive cannabinoids attach to CB1 receptors in the brain and nervous system** and cause the user to feel high. **CBD**, commonly referred non-psychoactive is mischaracterized and rather should be considered "**non-intoxicating or noneuphoric**" and can help calm the "high" of THC.

- **6 primary cannabinoids are: THC (Tetrahydrocannabinol), Tetrahydrocannabivarin (THCV), CBD (Cannabidiol), CBG (Cannabigerol), Cannabinol (CBN)** and **CBC (Cannabichromene)**

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# Cannabidiol (CBD)

- **Cannabidiol (CBD)** is a **phytocannabinoid** found in the cannabis species of plants, and the most common phytocannabinoid produced by hemp varieties of cannabis. **Commonly mischaracterized as non-psychoactive**, however, it is really **non-intoxicating/non-euphoric and lacking the associated reinforcement, craving, or compulsive use because it does not get the user "high". CBD DOES NOT impair** psychomotor, cognitive, sedative, **or** abusive characteristics. One unique characteristic of both CBD & THC is that they **won't cause repository, cardiac depression or death. Dr. Adie Poe, a neuroscientist out of St. Louis' Washington University said**, "Any substance that exerts its effects by directly impacting brain activity," she says, "is considered to be psychoactive".

- **CBD can be derived** from the hemp species of cannabis (i.e. industrial hemp); high CBD and typically **less** than 1% THC. **In the United States, defined as less than 0.3% THC** to be classified as hemp.

- **Cannabial** interacts with multiple systems: increasing the number of native cannabinoids in the human body; **binding with** serotonin receptors**, part of the "feel good" molecular machinery targeted by conventional S.S.R.I.s; and stimulating GABA receptors**, responsible for **calming the nervous system**. With more than 65 cellular targets, **CBD may provide a kind of full-body massage at the molecular level**.

- In the late 1990s, scientists at the National Institutes of Health discovered that CBD could produce **remarkable medicinal effects** neuroprotective antioxidants. In test tubes, the molecule shielded neurons from oxidative stress. That resulted in the **United States Department of Health and Human Services patenting** "A method of treating diseases caused by oxidative stress, comprising administering a therapeutically effective amount of a cannabinoid that has substantially no binding to the NMDA receptor to a subject who has a disease caused by oxidative stress"**.**
- CBD is a GPR55 antagonist, disclosed by Ruth Ross from the University of Aberdeen scientist **by blocking GPR55 signaling, CBD may act to decrease both bone reabsorption and** cancer cell proliferation**.**

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# Cannabidiol (CBD)

## Why almost ALL patients and consumers can benefit from CBD?

- **CBD is an incredible substance**. It is **2X as potent as a steroidal anti-inflammatory, like cortisone**, which is commonly used to treat arthritis,tendonitis, and bursitis. It is **10X stronger than salicylic acid**, which is a chemical typically used to treat acne." Upon administration, cannabidiol exerts its **anti-proliferative, anti-angiogenic and pro-apoptotic activity** through various mechanisms. **CBD stimulates endoplasmic reticulum (ER) stress and inhibits AKT/mTOR signaling, thereby activating autophagy and promoting apoptosis.**
- **Brightfield Group & HelloMD** conducted the **largest survey on cannabidiol covered 2400 patients** and found **42% of CBD users said they had stopped using traditional medications** like Tylenol pain relievers or prescription drugs like Vicodin and foundhad switched to using cannabis instead. **80%** said that they found the products to be **"very or extremely effective." Only 3%** or less found the product to be either ineffectual or only slightly effective.
- **Benefits of CBD**: Calms THC-induced high, decreases appetite, relieves migraines, reduces inflammation and helps relieve symptoms of psychotic disorders. Scientists have identified more than **60 different molecular pathways through which CBD operates**
- **CBD plays a critical role in its interactions with THC and can serve to help limit or decrease unwanted effects of THC**
- In studies, CBD has been shown to help decrease or eliminate some of THC's unpleasant adverse effects, modulating psych activity and reducing the incidence of THC induced sedation, anxiety, and rapid heartbeat.
- In other words, CBD can help "control the high" and prevent associated adverse events/reactions. **CBD induces changes in functional magnetic response (FMRI) the opposite of THC**.
- Since **CBD** helps maintain homeostasis of the ECS it can prevent recreational marijuana from "THC burnout".
- While THC provides the psychological effect on your mind, **CBD works** on a physiological level.
- **CBD vs. THC.**

- **The World Doping Committee (WADA )removed CBD from banned substances list in 2018.**

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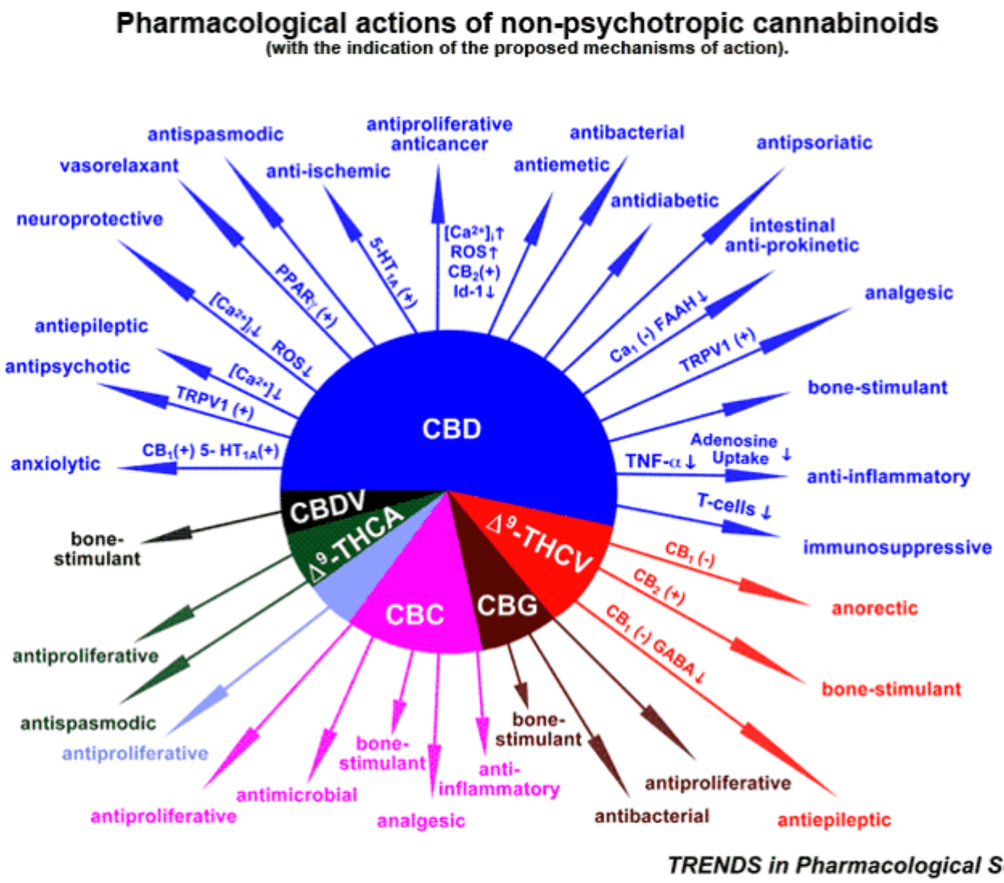
# Cannabidiol (CBD)

One unique characteristic of CBD & THC is that they won't cause repository, cardiac depression or death.




*TRENDS in Pharmacological Sciences*

**Through its interaction in the ECS**, and also with other phytocannabinoids ("Entourage" effect), **CBD has a very wide range of potential therapeutic applications: Potential disease processes that could benefit from CBD** (but not limited to):

- **Autoimmune diseases** (inflammation, rheumatoid - arthritis)
- **Neurological conditions** (Alzheimer's, dementia, Parkinson's, multiple sclerosis, epilepsy, Huntington's chorea, stroke, traumatic brain injury, concussion)
- **Metabolic syndrome** (diabetes, obesity)
- **Neuropsychiatric illness** (autism, ADHD, PTSD, alcoholism, anxiety, insomnia)
- **Gastrointestinal disorders** (Irritable Bowel Syndrome, Inflammatory Bowel Disease)
- **Skin disorders** - (acne, dermatitis, psoriasis)

CBD acts through multiple receptor-independent channels and it also binds to various receptors in the brain, including serotonin 5HT1A (which contributes to CBD's anti-anxiety effect), TRPV1 (which contributes to CBD's antipsychotic effect), the nuclear receptor PPAR-gamma (regulates gene expression), and the orphan receptor GPR55, among others. In studies at least 113 cannabinoids have been isolated from the cannabis plant. (and other plants as well...lichens, black pepper) in their carboxylic acid forms (THCA, CBDA, etc.). **CBDA, cannabidiolic acid, the raw non-psychoactive** cannabinoid **precursor to CBD, showed significant COX-2 enzyme blockage when compared to placebo**. CBDA converts to CBD through decarboxylation.

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# Why is CBD's role so important?

## Homeostasis of ECS

**Preclinical research and clinical studies have shown that CBD has strong anti-oxidant, anti-inflammatory, anticonvulsant, antidepressant, antipsychotic, and neuroprotective qualities.** CBD therapy is so appealing because of the huge number of the potential disease process and symptomatologies it can be used for.

Interacting with the ECS, **CBD's range of potential therapeutic applications has shown great promise is aiding:**

- **Autoimmune diseases** (inflammation, rheumatoid-arthritis)
- **Neurological conditions** (Alzheimer's, dementia, Parkinson's, multiple sclerosis, epilepsy, Huntington's chorea, stroke, traumatic brain injury, concussion)
- **Metabolic syndrome** (diabetes, obesity)
- **Neuropsychiatric illness** (autism, ADHD, PTSD, alcoholism, anxiety, insomnia)
- **Gastrointestinal disorders** (Irritable Bowel Syndrome, Inflammatory Bowel Disease)
- **Skin disorders** (acne, dermatitis, psoriasis)
- **Neutralization of free radicals**
- **Heart Health** improvement
- **Treating inflammation**

**CBD is disrupting the pharmaceutical industry it is clear that continuing clinical research is desperately needed**. Ongoing clinical research is happening at a rapid pace. **MD will be actively involved at the forefront of the research with the most innovative solutions available to address patients care**.

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# What can CBD treat? Case Studies

- **Epileptic Seizures:** CBD shows **anticonvulsant effects for partial seizures in the temporal lobe**, according to a study. Evidence from the study supports CBD as a potential therapeutic alternative for a range of human epilepsies. **CBD for children**.

- **Severe Neurological Diseases**: **Cannabidiol exerts anti-convulsant effects**. It can help treat severe neurological diseases such as multiple sclerosis, Alzheimer's and Parkinson's. CBD can **protect nerve cells from degenerative diseases**, researchers discovered, when breaking down their research to the molecular level. They refer to this as CBD's "**neuroprotective effect**" and is the cannabinoids most promising aspect. **Cannabinoids suppress inflammationry and neuropathic pain**.

- **Mood Disorders:** CBD effectively treats **PTSD** and other **mood disorderers**. It helps people to forget their traumatic memories. These are incredible findings which may help researchers figure out how CBD can treat other stress, anxiety disorders and **reducing the severity of PTSD symptoms**. **Cannabidiol as a Therapeutic Alternative for Post-traumatic Stress Disorder**.

- **Anxiety- In studies, CBD was effective against anxiety and panic attacks. CBD's broad pharmacological profile, including interactions with receptors known to regulate fear and anxiety-related behaviors. Its anxiolytic-like properties are similar to those of diazepam.**

- **Depression: Endocannabinoid Signaling in the Etiology and Treatment of Major Depressive Illness . Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission**.

- **Chronic Pain:** THC plays a big role in this category, but CBD is also a powerful painkiller. **Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors. Cannabinoids may offer significant "side benefits" beyond analgesia**.

- **Inflammatory Bowel Disease: Cannabinoids are currently being used to treat inflammatory bowel disease and has been success in treating Crohn's Disease as well as reducing intestinal inflammation**.

- **Nausea: Cannabidiol attenuates vomiting and nausea-like behavior. Regulation of nausea and vomiting by cannabinoids**.

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# Case Studies

- **Addiction**: Over **21.5 million** Americans need therapeutic treatment for addiction. **400k Americans have died of opioid-related deaths since 2000.**
- **CBD has been shown to regulate stress response and compulsive behavior.**
- CBD has been shown to reduce anxietyy and prevent the development of high impulsivity for the prevention of relapse to drug use. Cannabidiol reduces cigarette consumption in tobacco smokers resulting in smoking 40% less. CBD relevance for treating anxiety-related and substance abuse disorders.
- CBD as an intervention for addictive behaviors.
- Cannabidiol Counteracts Amphetamine-Induced Neuronal and Behavioral Sensitization.
- CBD attenuates experimental anxiety in rats with alcohol and cocaine histories.
- **Opioid Addiction:** Some evidence even shows one of the primary components in cannabis, cannabidiol (CBD), halts the **cravings consistent with opioid dependence.** Development of Cannabidiol as a Treatment for Addiction.
- Cannabidiol inhibits the reward-facilitating effect of morphine.
- **Diabetes**- CBD-treatment inhibits diabetes by induction of regulatory Th2 responses.
- **Insomnia & Sleep**: Endocannabinoid Modulation of Cortical Up-States and NREM Sleep. Cannabidiol modulates sleep. According to the **National Sleep Foundation**, 30-40% of American adults report symptoms of insomnia within the last 12 months, and 10-15 percent of adults claim to have chronic insomnia. Endocannabinoid Signaling Regulates Sleep Stability. The Canadian Forces Health Services Operational Trauma and Stress Support Centre in Ottawa outpatient study on medical marijuana to treat individuals with PTSD-related nightmares who were given nabilone, "an endocannabinoid receptor agonist." The study found that 72% of the patients had far fewer nightmares or stopped having them altogether lover the course of their treatment. Some of the patients also saw benefits in their amount of sleep and their waking PTSD symptoms, such as flashbacks and hypervigilance.
- **Acne- CBD is ten times stronger than salicylic acid**, which is a chemical typically used to treat acne." CBD's effects on the endocannabinoid system can prevent acne and help clear up skin conditions.

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# Case Studies

- **Cancer:** Trials show CBD has a potent anti-tumor effect. CBD slows the progression of certain cancers like lung, breast, colon and prostate cancer. CBD is a potent inhibitor of both cancer growth and spread. Cannabidiol has the potential of an anticancer drug.

- **Fibromyalgia:** The Consumption of Cannabis by Fibromyalgia Patients in Israel.

- **Stress:** CBD helps reduce stress and improve mood by gently and naturally calming your overactive mind.

- Endogenous cannabinoid signaling is essential for stress adaptation.
- Cannabinoids Ameliorate Impairments Induced by Chronic Stress.
- Cannabinoid Receptor Activation Prevents the Effects of Chronic Mild Stress on Emotional Learning.

- **Osteoporosis: Affects over 53 million Americans**. CB2 receptors are present in bone tissue play and **play a role in bone metabolism** regulation helping to maintain balance.

- Cannabinoid Receptors as Target for Treatment of Osteoporosis.
- Cannabinoid receptors and the regulation of bone mass.
- Cannabinoid Receptor Type 1 Protects against Age-Related Osteoporosis.

- A Cross-Sectional Study of Cannabidiol Users.

- **Other studies:** Effects of acute systemic administration of cannabidiol.

- **Acne- CBD is ten times stronger than salicylic acid**, which is a chemical typically used to treat acne." CBD's effects on the endocannabinoid system can prevent acne and help clear up skin conditions.

Cannabis-based medicine is a rapidly emerging field of which all pain physicians need to be aware .

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# Case Studies, Data, & Statistics

**When the body is unable to produce endocannabinoids in the concentrations required, chemical imbalances occur, which can lead to illness.**

- **The CDC estimates nearly 50 million Americans or approximately 28% of adults have chronic pain.**
- **Nearly 18 million Americans are taking opioids.**

- **NIH estimates 46.6 million U.S. adults live with a mental illness**. Studies found that some people with low endocannabinoid levels are more prone to addiction. **Anxiety disorders affect 40 million people** in the US. **CBD could reduce anxiety beyond placebo levels. Cannabidiol as a Potential Treatment for Anxiety Disorders**. **Mental Health America found that 27% of senior citizens suffer from severe anxiety disorders**.

- **Around 39 million Americans are affected by migraines, according to the Migraine Research Foundation. Center of Disease Control (CDC) estimates 49.6% of seniors have arthritis.**

- **One in five (21%) adults worldwide are diagnosed with some form of arthritiss by their physicians (Helmick et al., 2008)**.

- **Leading expert Dr. Ethan Russo found that endocannabinoid system changes could help to alleviate migraines in his 2004 research**. The main finding was that anandamide, a key neurotransmitter in the ECS, heightens the effectiveness of the 5-HT1A receptor while inhibiting the 5-HT2A receptor.

- **Harvard NeuroDiscovery Center estimates that 5 million Americans suffer from Alzheimer's disease; 1 million from Parkinson's; 400,000 from multiple sclerosis (MS); 30,000 from amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), and 30,000 from Huntington disease**.

- **NIH estimates nearly one in five U.S. adults live with a mental illness (46.6 million in 2017)**.

- **Dementia** currently affects over **35 million** people worldwide

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# Inflammation

"All disease starts with cellular inflammation".
-Dr. Keith Nemec, Director of Total Health Institute

**"Whether you have cancer, heart disease, diabetes, digestive disorders, autoimmune disease or Alzheimer's, it all starts with inflammation at the cellular level which leads to either early cell death translating into a specific organ or gland disease or into cancer stem cell stimulation which fuels cancer cell growth and metastasis."**

Prof. Prakash Nagarkatti, VP of Research at the University of South Carolina whose laboratory studies endocannabinoid regulation of immune responses research demonstrates that **endocannabinoids are produced upon activation of immune cells and may help regulate the immune response by acting as anti-inflammatory agents.** "Thus, interventions that manipulate the metabolism or production of endocannabinoids may serve as a novel treatment modality against a wide range of inflammatory disease."

- **Inflammation:** CBD is an incredible substance and is valued for treating inflammation. It is twice as potent as a steroidal anti-inflammatory, like cortisone, which is commonly used to treat arthritis, tendonitis, and bursitis.

- CBD has its own special anti-inflammatory qualities — it binds with your ECS to generate a response to reduce nerve inflammation. Cannabinoid Delivery Systems for Pain and Inflammation Treatment.
- Cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis.
- **Consumers trends have moved from "lets cure" to "preventive" measures. CBD is having a profound effect on healthcare**.

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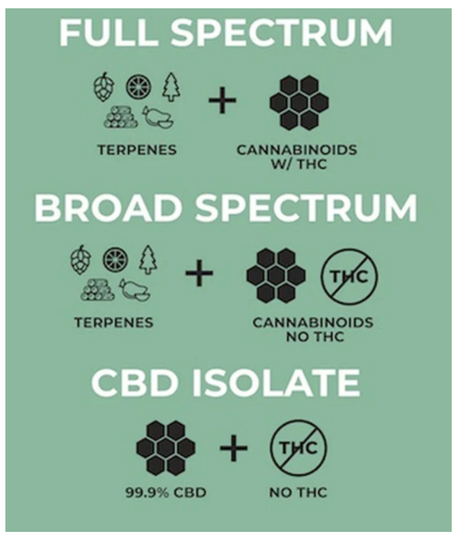
# Routes of Administration

**Combining formulations may provide an opportunity to produce rapid systemic effects and long-term outcomes (e.g., analgesia)**

**It is important to understand the terminology differences between CBD and MMJ based products/medications.**

**Types of CBD products available:** Full Spectrum vs Broad Spectrum vs Isolate products.

- **Full Spectrum** = extract contains all compounds found naturally occurring in the plant (all cannabinoids, terpenes, etc.) INCLUDING THC.
- **Broad Spectrum** = extract that contains all compounds found naturally occurring in the plant (all cannabinoids, terpenes, etc.) EXCLUDING THC.
- **Isolate** = purest form of a compound (i.e. CBD) removing all other compounds found in the plant




**CBD is easily accessible for all consumers**

- You do not need a specific diagnosis or medical marijuana card to undertake CBD based therapies….gentle entry point into medical cannabis-based therapies.
- **CBD Vs. THC**
- **CBD: THC ratios**
- **Many CBD myths and misconceptions still exist.**

**The way cannabis is delivered is *key* to its medicinal properties.**

**Inhaled route** *(vaporized, nebulized)*
RAPID onset (within a few minutes)
SHORT duration (typically lasts for 1-2 hrs.)
Good for rapid-acting symptom relief

**Ingested/Oral route** (*oils, tinctures, capsules, edibles, etc.*)
DELAYED/SLOW onset (typically 30-90 mins…up to 120)
LONG duration (typically lasts 6-8 hrs.)
Buccal or Sublingual (under cheek or tongue) helps to increase the rate of absorption through the oral mucosal lining (i.e. can make an oral taken solution work more quickly)

**Topical route** (*gels, creams, lotions, etc.*)
Onset is mid-range, approximately 20-30 mins
Duration is mid-range as well, typically 1-3 hrs.
MINIMAL SYSTEMIC ABSORPTION
Topical (designed to work locally) is DIFFERENT than transdermal (designed to get into the bloodstream)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# Treating Patients – Dosing… there is no "Gold Standard"….yet

Instructions should be provided by a qualified licensed medical professional

## Dosage Methods

- **There is no lethal dose of cannabis or cannabidiol** (no dose that will result in death)
- **Once absorbed**, 90% of cannabinoids will be bound to proteins in the blood plasma.
- **Initial metabolism of cannabinoids** largely takes part in the liver via the CYP450 enzymatic pathway.
- This **same pathway** is used in the processing of many OTC and prescription medications (i.e. some anticoagulants and anti-convulsants)
- **Using medications which are processed by the same pathway as cannabinoids can result in increased or decreased effects of said medications as well as cannabis-based medications/products**
- **Patients should always discuss with their physician or pharmacist regarding potential medication interactions**
- (www.drugbank.ca)

## Process & metabolism

- **Start "Low & Slow"…** slowly increasing (or titrate) to the desired effect for ALL patients/consumers.
- **Frequency -** depends on the patient, goal of therapy, and route of administration.
- **Combining multiple routes of administration** (i.e. using an oral+ topical CBD preparation) can be more effective than a single route of administration.
- Different disease processes/symptomatology = **different treatment regimens**
- Because of the lack of gold standard regarding dosing and administration, treatment is both an art and a science.
  - The patient needs to have dosing titrated in the appropriate manner
  - The patient needs to be closely followed
  - Dosing can vary based on the route of administration
  - Guided by a provider with scientific AND clinical knowledge

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# Contraindications

**DRUGS THAT CAN *INCREASE* THE EFFECTS OF ORALLY ADMINISTERED CANNABIS**

**Amiodarone (Cordarone):** treating cardiac arrhythmias

**Clarithromycin (Biaxin):** antibiotic

**Diltiazem (Tiazac, Cardizem, Dilacor):** treating high blood pressure, angina

**Erythromycin (Robimycin, Ilosone, Acnasol):** antibiotic

**Fluconazole (Diflucan, Trican):** antifungal

**Isoniazid (Nydrazid, Rifamate):** treating tuberculosis

**Itraconazole (Sporanox):** antifungal

**Ketoconazole:** antifungal

**Miconazole (Monistat):** over-the-counter antifungal

**Ritonavir (Norvir):** HIV protease inhibitor

**Verapamil (Calan, Veralan, Isoptin):** treating cardiac arrhythmias

**DRUGS THAT CAN *DECREASE* OR INTERFERE WITH THE EFFECTS OF ORAL CANNABIS**

**Carbamazepine (Tegretol, Equetro, Carbetrol):** anticonvulsant

**Phenobarbital:** sedative, anticonvulsant

**Phenytoin (Dilantin):** anticonvulsant

**Primodone (Mylosine):** anticonvulsant

**Rifabutin (Mycobutin):** Mycobacterium avium complex (MAC) disease

**Rifampicin (Rifampin, Rifadin, Rifater, Rimactane):** antibiotic

**St. John's Wort:** herbal antidepressant

Additionally, cannabis medicines (smoked, oral, sublingual, or vaporized) increase the effects of alcohol, benzodiazepines (Ativan, Halcion, Librium Restoril, Valium, Xanax, etc.), and opiates (codeine, fentanyl, morphine, etc.).

Some people experience side effects of CBD. The side effects, however, tend to vary from one individual to another based on their genetic predisposition and dosage. **Drug interactions are important to consider as it can have serious impacts on a patient's treatment and wellbeing**. The most common side effects in limited cases are Nausea, fatigue and irritability.

**1. Effects of Drug Metabolism**

CBD causes **inhibition of hepatic drug metabolism** and a decrease in p-glycoprotein activity in some people. CBD **may interact with some medications** and treatments. CBD can increase the level in your blood of the blood thinner Coumadin, and it can raise levels of certain other medications in your blood by the exact samea mechanism that grapefruit juice does. Also, in response to CBD use, cytochrome P450 (liver enzymes) reduce their activity. These liver enzymes are extremely important for your body to function properly, since they are responsible for metabolizing the medications you take to treat your health condition.

**2. Causes Dry Mouth**

Some individuals report dry mouth after administering CBD. It's only a minor side effect involving the endocannabinoid that reduces saliva production.

**3. Increase Some Symptoms of Parkinson's Disease in High Doses**

When it comes to CBD's effect on treating Parkinson's disease, there are contradictory results. According to some research, **CBD may increase muscle movement and tremor intensity in high doses**. Others show the body tolerates CBD well and **may be beneficial in treating Parkinson's disease** or similar diseases.

**An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies**

# CBD Hurdles

- **CBD is a booming business** right now but has many hurdles to build consumer confidence., Additionally, in part due to **recent legislation on a federal level**, Hemp derived Cannabidiol **(CBD) is readily available** to consumers across the United States and provides an easily accessible entry point into medical cannabis-based therapies, even for patients without a traditional "qualifying diagnosis". Many different brands, many routes of administration creating confusion among consumers. Now you can get CBD at the local gas station!!!
- **The problem:**
  - Many products produced outside the US (i.e. China) with **little regulatory control**.
  - Products are not what they say on the label. In fact, it is **estimated that 83% of CBD sold does not contain** the active ingredients they promise or were mislabeled. If the product doesn't come with a **Certificate of Analysis (COA)** it shouldn't be purchased.
  - Contamination with toxic by-products or chemicals.
  - Patients/Consumers have **no real guidance** on **HOW** to consume.
  - **Failure rates** can be high as a result and consumers can lose confidence.
- **To ensure purity, consistency, and safety, ALL of our CBD PRODUCTS are sourced in the USA, Organic and triple lab tested**. Beware of what people are selling isn't always what you receive and can, therefore, be a liability as well as hurt your credibility. Purchase from a **trusted name with a proven track record**.
- Most CBD companies have minimal to no clinical research on their products, and not actively collecting data.
- **No Warning Letter** has been issued by the FDA to a company that merely sold legitimate hemp-derived CBD products without making inappropriate disease-remediation claims.

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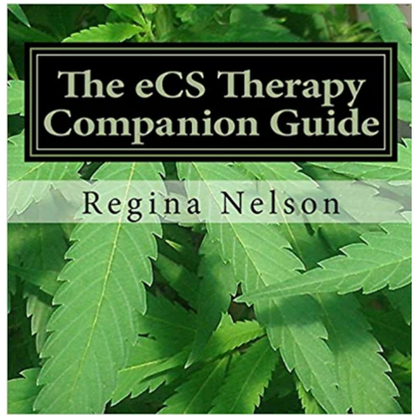


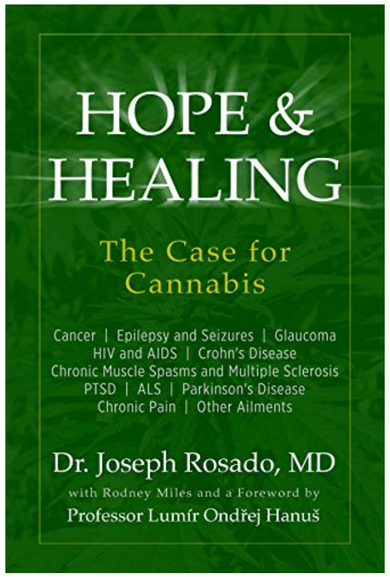


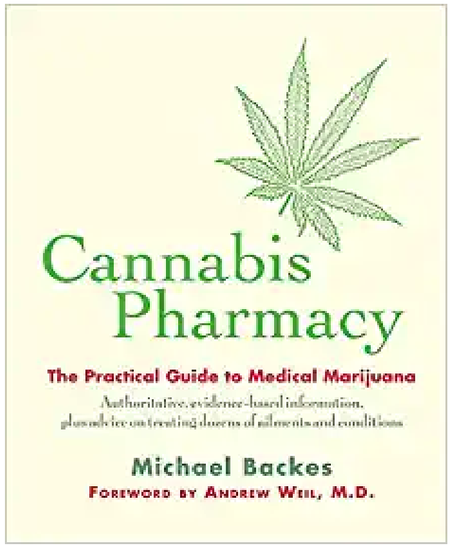


# REFERENCES & RECOMMENDED RESOURCES

- **Cannabis Pharmacy –** Michael Backes
- **The ECS Therapy Companion Guide –** Regina Nelson
- **Hope & Healing – The Case for Cannabis –** Dr. Joseph Rosado
- **Americans for Safe Access –** https://www.safeaccessnow.org/
- **Project CBD -** https://www.projectcbd.org/
- **PubMed/NIH Database (**https://www.ncbi.nlm.nih.gov/pubmed/**)**
- CBD Legal Guidelines state by state
- Americans for Safe Access- Medical Cannabis in America
- Marijuana Resources of Medical Conditions

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