Introduction to Hemp and Cannabinoids

Cannabis has been used for hundreds of years, with the earliest documented use dating back to the ancient era over 2,000 years ago. Despite clear evidence for its medicinal, agricultural, and industrial usefulness, however, cannabis's more modern history of legal prohibition and misinformation pushed it out of the scientific and medical spotlight for many decades. With the advent of cannabis-based medicines such as Sativex and Epidiolex, plus heightened societal, medical, scientific, and political interest, cannabis is more in the spotlight than ever before. The information disseminated around cannabis, cannabinoids, and the endocannabinoid system must be clear, accurate, and evidence-based.

The following background materials are intended to cover the science and biology of cannabinoids, their effect on the human body, and their uses in plain language for those who want a better understanding of where therapeutic cannabinoids such as CBD come from, how they work, and other uses for the cannabis plant (such as hemp fiber for clothing. This article will introduce the correct terminology, historical context, pharmacology, clinical indications, and ongoing research of cannabinoids. Many of these topics will be explored in greater detail in other background articles.

An Introduction to Hemp

Cannabis L. is a genus of plants in the family *Cannabaceae Endl.* that includes hops and hackberries. Cannabis plants produce unique metabolites known as ***phytocannabinoids***, which belong to the larger category of cannabinoids, and are naturally occurring compounds that are found in plants and animals. Cannabinoids that are naturally produced by plants are referred to as phytocannabinoids. Over 100 unique phytocannabinoids have been identified in the cannabis plant, though many are produced in trace quantities[1]. Cannabinoids produced in the human body are referred to as ***endocannabinoids*** for endogenous cannabinoids. Scientists are also able to produce ***synthetic cannabinoids*** in laboratories.

Naming: Indica, Sativa, and Ruderalis

It has been common to separate the cannabis plant into three species: Cannabis indica, Cannabis sativa, and Cannabis ruderalis, but this categorization is false. While there is a great breadth of variety within the Cannabis genus, there is no chemical or biological basis underlying the indica, sativa, and ruderalis distinctions despite nonscientific claims otherwise. Scientists prefer to classify all Cannabis plants as one species, with distinctions based entirely on the biochemical composition of the plant (meaning proportion of various compounds found within the plant)[2,3].

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[1] Aizpurua-Olaizola, O., Soydaner, U., Öztürk, E., et al. Evolution of the cannabinoid and terpene content during the growth of *Cannabis sativa* plants from different chemotypes. J. Nat. Prod. 2016;79(2):324–331. https://doi.org/10.1021/acs.jnatprod.5b00949

[2] Piomelli, D., Russo, E.B. The *Cannabis sativa* versus *Cannabis indica* debate: An Interview with Ethan Russo, MD. Cannabis Cannabinoid Res. 2016;1:44–46. https://doi.org/10.1089/can.2015.29003.ebr

[3] Lewis, M.A., Russo, E.B., Smith, K.M. Pharmacological foundations of cannabis chemovars. Planta Medica. 2017;84:225–233. https://doi.org/10.1055/s-0043-122240

The Real Difference Between Marijuana and Hemp

Marijuana is a term that has been used to describe cannabis used recreationally and refers to cannabis that has been bred to have high levels of delta-9-tetrahydrocannabinol (THC), a psychoactive cannabinoid that has an intoxicating effect. ***Hemp*** is a term that has been used to describe cannabis plants that do not have high THC content and that are cultivated for fiber and seeds that can be used in the production of a wide range of products.

Because cannabis was historically cultivated for use in materials such as rope, fabric, and paper, *hemp* is sometimes defined as "fiber-type" cannabis. This colloquial distinction between "drug-type" and "fiber-type" cannabis is a misnomer in that both plant types belong to the cannabis family. The false dichotomy is based more on perception than it is on the actual phytocannabinoid content of any plant. While "marijuana" and "hemp" are from the same plant family, they name two different types of cannabis that have been grown over time and bred to emphasize their distinct properties: "marijuana" has come to refer to cannabis plants selectively bred for their high THC content, while "hemp" plants are cannabis plants with very low THC content that have been bred for the fiber and seeds they produce. In this background article, we will use the scientifically correct term of *cannabis* to refer to all mentions of the plant.

There are thousands of individual cannabis types containing varying concentrations of cannabinoids and other phytochemical compounds, with the relative proportions of these metabolites being the primary determinant of a plant's effects. The term ***strain*** has been used to differentiate individual cannabis plants, but this is another misnomer. *Strain* is an appropriate term for distinctions in bacteria or viruses, but the terms ***chemovar*** or ***cultivar*** are the technically

correct terms used in plant science[4]. The term "strain," however, has become commonly used to distinguish individual cannabis types.

Cannabinoids and Terpenes

The cannabis plant contains a vast number of chemical compounds, both housed within its leaves and stems, as well as in its resinous secretions. These are the active agents of cannabis's effects, both therapeutic and adverse. The most interesting of these compounds are the phytocannabinoids and terpenes.

Phytocannabinoids

Phytocannabinoids are a class of chemical compounds produced by cannabis plants. Phytocannabinoids and the larger family of cannabinoids are substances that can bind and activate a specific group of membrane receptors called cannabinoid receptors that are found in vertebrates. Chemically, cannabinoids are lipophilic, meaning "fat-loving." As such, they can dissolve in fats, oils, and other nonpolar substances such as hexane and ethanol. (Nonpolar refers to the chemical structure of substances such as fats, lipids, waxes, and alcohols that are not dissolvable in water.) Cannabinoids have demonstrated a remarkable safety profile; to date, cannabis on its own has not resulted in a single fatality[5].

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[4] Lewis, M.A., Russo, E.B., Smith, K.M. Pharmacological foundations of Cannabis chemovars. Planta Med. 2018; 84(04):225-233. http://dx.doi.org/10.1055/s-0043-122240

[5] Calabria, B., Degenhardt, L., Hall, W., Lynskey, M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug Alcohol Rev. 2010;29(3):318–30. https://doi.org/10.1111/j.1465-3362.2009.00149.x

Cannabis has been used and cultivated since ancient times as an industrial material and as a medicinal treatment. For centuries, cannabis was a widely accepted plant material lauded for its multitude of uses before misinformation and negative propaganda changed public and political sentiment in the 1900s.

Discovery of the Endocannabinoids

As a result of the political climate of the last 100 years, much of the most significant cannabis research of the 20th century was completed outside of the United States. THC was first identified and isolated in a laboratory in Israel in 1964, followed swiftly by the discoveries of CBD, CBC, CBDV, and THCV before the 1960s ended. The first cannabinoid receptor in the body, CB_1, was discovered in 1988, only to be upstaged in 1995 by the remarkable discovery of the human body's own naturally occurring endogenous cannabinoids (**endocannabinoids**): anandamide (AEA) and 2-arachidonoylglycerol (2-AG)[6].

A Closer Look at Cannabinoids and What They Do

The cannabinoids that are found in the highest concentrations in cannabis plants are tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), cannabinolic acid (CBNA), cannabigerolic acid (CBGA), and cannabichromenic acid (CBCA)[7]. These acidic phytocannabinoids are converted to their biologically active forms (e.g., THC, CBD, CBN, CBG, and CBC, respectively) through the process of decarboxylation, wherein a carboxyl group

[6] Russo, E.B. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163(7):1344-1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x

[7] Andre, C.M.; Hausman, J.-F.; Guerriero, G. Cannabis sativa: The Plant of the Thousand and One Molecules. Front. Plant Sci. 2016, 7, 19.

is released from the compound. In cannabis production, decarboxylation is achieved by heating the plant material to a specific temperature or through exposure to sunlight.

THC

THC is the most common phytocannabinoid in cannabis cultivars (also called chemovars, or in nonscientific terms, strains). THC is a partial agonist of CB_1 and CB_2 receptors (just as the endocannabinoid AEA is). It exhibits potent psychoactivity and causes intoxication characterized by feelings such as euphoria, lightheadedness, and disruption of time perception. While these properties are what recreational users seek, the intoxicating effects of THC are considered adverse effects in a therapeutic context. THC has demonstrated several beneficial activities as an analgesic, muscle relaxant, antispasmodic, and anti-inflammatory substance, demonstrating 20 times the inflammation-reducing power of aspirin and 2 times that of hydrocortisone[8,9].

Although patients taking THC can build up a tolerance to its psychoactive effects (i.e., need higher doses for the same effect), research has shown that patients do not develop a tolerance to its therapeutic benefits—this is a stark difference from opioids. Opioids are dangerous because at higher doses, respiratory function becomes depressed and people can die from an opioid overdose. For THC, attainment of therapeutic benefit does not require attainment of THC's euphoric effects. While THC is the only cannabinoid that patients can become dependent on (again, in the context of its intoxicating effects and defined by the National Institute on Drug Abuse as when "a person feels withdrawal symptoms when not taking the

[8] Pacher P, Batkai S, Kunos G (2006). The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 58:389–462.
[9] Evans FJ (1991). Cannabinoids: the separation of central from peripheral effects on a structural basis. Planta Med 57: S60–S67.

drug"), studies so far have shown that patients do not develop a tolerance to the therapeutic benefits of cannabinoids.

In medicine, the goal is to increase the therapeutic effect or effects while reducing the number or degree of adverse effects experienced. This goal has catalyzed increased interest in CBD-predominant cultivars as well as THC formulations in concert with other cannabinoids.

CBD

CBD is another common phytocannabinoid. In cultivars not dominated by THC, it is the most prevalent cannabinoid. CBD is frequently mischaracterized in both popular and scientific descriptions as "nonpsychoactive" because it does not have an *intoxicating* effect. The term "psychoactive," synonymous with "psychotropic," describes that a compound affects the mind, which CBD certainly does. It has demonstrated prominent benefits on conditions such as anxiety, schizophrenia, addiction, and possibly depression[5]. Intoxication, on the other hand, refers to markedly reduced physical or mental control, or both. While CBD acts on the mind, it does not reduce a person's mental or physical capacities, so it's more accurate to label CBD as non-intoxicating[10].

CBD has been reported to have anxiolytic, antipsychotic, analgesic, and anti-inflammatory properties. It has also demonstrated the ability to reduce many of the effects which limit THC's therapeutic efficacy such as anxiety and tachycardia (rapid heart rate). CBD achieves this through a process called negative allosteric inhibition at the CB_1 receptor, where CBD binds to a different part of the CB_1 receptor, resulting in a change to the receptor's shape that makes it more difficult for THC to bind. CBD is also able to inhibit the uptake of AEA, an

[10] Russo, E.B. Cannabidiol claims and misconceptions. Trends Pharmacol Sci. 2017 Mar;38(3):198-201. Erratum in: Trends Pharmacol Sci. 2017 May;38(5):499. https://doi.org/10.1016/j.tips.2016.12.004

endocannabinoid that is an important neurotransmitter in the central and peripheral nervous systems[11].

CBD has been widely studied and validated as a potent treatment to reduce seizures in people with seizure disorders such as Lennox Gastaut syndrome, Dravet syndrome, and tuberous sclerosis. After multiple comprehensive clinical studies on its safety, effectiveness, and tolerability, pure CBD has received FDA approval as a treatment for seizures in children. Children are notoriously difficult to treat because they cannot tolerate the side effects of other medications, but pure CBD can help children with rare seizure disorders who have not been treated successfully by other therapies[12,13].

Other Cannabinoids: CBG, CBC, and CBN

CBG

Cannabigerol (**CBG**), was the first cannabinoid identified. CBG has antibiotic, antifungal, anti-inflammatory, and analgesic effects[5]. A 2006 study found CBG to be the second most effective phytocannabinoid (with CBD being the most effective) against breast cancer cells in a laboratory setting using cell lines to look at cell death in tumor cells[14]. Like CBD, CBG is

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[11] Bisogno, T., Hanus, L., De Petrocellis, L., et al. Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001;134:845–852. https://doi.org/10.1038/sj.bjp.0704327

[12] Devinsky, O., Patel, A.D., Cross, J.H., et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. N. Engl. J. Med. 2018;3781:888-1897. https://doi.org/10.1056/NEJMoa1714631

[13] Szaflarski, J.P., Bebin, E.M., Cutter, G., et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. Epilepsy Behav. 2018 Oct;87:131-136. https://doi.org/10.1016/j.yebeh.2018.07.020

[14] Ligresti, A., Moriello, A.S., Starowicz, K., et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther. 2006 Sep;318(3):1375-87. https://doi.org/10.1124/jpet.106.105247

able to inhibit uptake and consequently increase overall levels AEA[15]. CBG's acidic form, CBGA, is a precursor molecule for several of the primary cannabinoids including THC, CBD, and CBC.

CBC

Cannabichromene (**CBC**) has demonstrated antidepressant, anti-inflammatory, antibiotic, antifungal, and analgesic qualities, as well as the ability to strongly inhibit AEA uptake[5,14].

CBN

Cannabinol (**CBN**) is a phytocannabinoid that is produced by the degradation of THC. Initially, it was observed in higher concentrations in cannabis that had been harvested, then improperly stored, and left exposed to heat and light. Under such conditions, THC decomposes to form the cannabinoid CBN. Because CBN is a metabolic product ("metabolite") of THC, it is found in relatively small concentrations in live cannabis plants where THC degradation occurs much less readily. CBN has demonstrated sedative and anticonvulsant activity and has been shown to have significant anti-inflammatory, antibiotic, and anti-MRSA activity[5]. MRSA is a type of bacteria that is resistant to many of the antibiotics healthcare professionals use to fight infections. CBN has shown promise as a therapeutic compound in topical applications for skin issues such as psoriasis and burns and has been shown to modulate the activity of many important enzymes and types of cells, such as stem cells[16].

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[15] De Petrocellis L, Ligresti A, Schiano Moriello A, et al. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: Pro-apoptotic effects and underlying mechanisms. *Br J Pharmacol*. 2013;168(1):79-102. https://doi.org/10.1111/j.1476-5381.2012.02027.x

[16] Russo, E. B., & Marcu, J. (2017). Cannabis pharmacology: The usual suspects and a few promising leads. *Advances in Pharmacology*, *80*, 67–134. https://doi.org/10.1016/bs.apha.2017.03.004

Endogenous and Synthetic Cannabinoids

In addition to the cannabinoids found in the cannabis plant, scientists have discovered an endogenous class of cannabinoids in the human body that function as neurotransmitters. Scientists have also developed synthetic cannabinoids including nabilone, HU-211, and ajulemic acid. These discoveries and developments add to the number of cannabinoids to investigate, as scientists around the world continue to elucidate how these compounds work and how they might benefit human health and well-being.

Terpenes

Terpenoids, more commonly referred to as **terpenes,** are the largest category of plant molecules, comprising nearly 20,000 compounds[17]. These essential oil components are not exclusive to cannabis and are also found in many herbs, spices, fruits, and plants such as lavender, citrus, rosemary, and vanilla, giving these plants their signature scents. Terpenes are the molecular foundation of the huge spectrum of flavors and scents found in the natural world. The manipulation and combination of terpenes can produce unique flavors and aromas, but terpenes themselves have a range of therapeutic effects that make them far more than aesthetic agents of taste and smell. Terpenes are potent and can affect animal and human behavior at low levels, offering a rich profile of relaxing, antiseptic, antiviral, and anti-inflammatory properties. Herbalists and apothecaries have used terpenes for centuries in herbal and natural remedies for aromatherapy or nontoxic disinfection, for example.

[17] Langenheim J.H. (1994). Higher plant terpenoids: A phytocentric overview of their ecological roles. *Journal of Chemical Ecology*, *20*(6), 1223–1280. https://doi.org/10.1007/BF02059809

Terpenes, not cannabinoids, are what lend each cannabis cultivar its particular blend of fragrant odors. Terpenes make up 10% of the phytochemical content of trichomes, the primary cannabinoid-producing structures on the cannabis plant; terpenes are what determine the viscosity of the cannabinoid-rich resin that the plant secretes. It has also been thought that terpenes modulate the medicinal effects of cannabinoids. Though there have been up to 200 different types of terpenes characterized in the cannabis plant, scientists and growers already have a key group of terpenes that they have homed in on as targets for research. Terpenes of interest include limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol[18]. These terpenes are all recognized as safe by the U.S. Food and Drug Administration.

The Endocannabinoid System

All cannabinoids interact with the body through the endogenous cannabinoid receptor system, called the **endocannabinoid system (ECS)** for short. This system includes the cannabinoid receptors, endocannabinoids, and the enzymes involved in the synthesis, transport, and degradation of cannabinoids[19]. Activation of the ECS can trigger a cascade of signals and effects, causing physical and chemical changes that result in changes in one's physical and mental states.

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[18] Adams, T.B., & Taylor, S.V. (2010). Safety evaluation of essential oils: A constituent-based approach. In K.H.C. Baser & G. Buchbauer (Eds.), *Handbook of essential oils: Science, technology, and applications* (pp. 185–208). CRC Press.

[19] Bolognini, D., Rock, E.M., Cluny, N.L., Cascio, M.G., Limebeer, C.L., Duncan, M., Stott, C.G., Javid, F.A., Parker, L.A., & Pertwee, R.G. (2013). 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), 1456–1470. https://doi.org/10.1111/bph.12043

Cannabinoids, which have different binding affinities for the cannabinoid receptors, selectively bind and enact their pharmacologic effects depending on where the receptors they bind to are located in the body. CB1 receptors are found in the highest concentration in the central nervous system, but have also been identified in peripheral nerve endings and non-neural tissues such as fat, lungs, liver, spleen, bladder, prostate, testicles, and stomach[18]. In the brain, CB1 receptors are particularly expressed in regions that are associated with motor function, emotion, perception, and endocrine function[20]. CB2 receptors generally are present in immune tissues, although they are also found in the central nervous system and play a crucial role in regulating the body's immune response[21].

How It All Works Together: the Entourage Effect

The ***entourage effect*** describes a theory that the combination of various cannabinoids and terpenes evoke stronger therapeutic benefits than are possible with any single compound alone. Research has shown that cannabinoids and terpenes work together in complementary pharmacological ways, improving the overall therapeutic usefulness of formulations that contain a larger spectrum of phytocompounds from the cannabis plant. For instance, terpenes are known to modulate the absorption of cannabinoids by increasing the permeability of the blood-brain

[20] National Academies of Sciences, Engineering, and Medicine. (2017). *The health effects of Cannabis and cannabinoids: The current state of evidence and recommendations for research*. The National Academies Press. https://doi.org/10.17226/24625

[21] Hill, M.N., Bierer, L.M., Makotkine, I., Golier, J.A., Galea, S., McEwen, B.S., Hillard, C.J., & Yehuda, R. (2013). Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. *Psychoneuroendocrinology*, *38*(12), 2952–2961. https://doi.org/10.1016/j.psyneuen.2013.08.004

barrier and of the skin layer (the latter being relevant to topical and/or transdermal application of cannabinoids). CBD is well-known to counteract the adverse effects of THC such as disorientation and disrupted cognition, while other cannabinoid combinations have been shown to strengthen the therapeutic effects far beyond what would be expected from an additive mechanism[22].

Cannabinoid Extraction – Full Spectrum, Broad Spectrum, and Isolated Cannabinoids

Cannabinoid extraction involves the use of various physical or chemical techniques, or both, to separate cannabinoids from raw harvested plant mass and produce an oil with as pure a cannabinoid content as possible. Cannabinoid extracts can be described as made from full spectrum, broad spectrum, or isolated cannabinoids.

Full Spectrum Extracts

Full spectrum extracts include the whole range of cannabinoids and terpenes found in the cannabis plant. Full spectrum extracts are said to take full advantage of the entourage effect, whereby the overall combined effects of the cannabinoids and terpenes are greater than the results of any single compound. Along with CBD, full spectrum products will include minor cannabinoids such as CBN, CBG, and CBC, as well as the major cannabinoid THC (but at a level less than 0.3%, so this low level of THC shouldn't be enough to cause any psychoactive

[22] Herkenham, M., Lynn, A.B., Little, M.D., Johnson, M.R., Melvin, L.S., de Costa, B.R., & Rice, K.C. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(5), 1932–1936. https://doi.org/10.1073/pnas.87.5.1932

effects unless the full spectrum extract is taken in large servings). Full spectrum CBD products, however, could cause someone to fail a drug test.

Broad Spectrum Extracts

Broad spectrum extracts are produced by completing an additional extraction step to full-spectrum products to remove the majority of cannabinoid and terpene content. Broad-spectrum CBD is like full-spectrum CBD in that it features a profile of several phytocannabinoids, but broad spectrum CBD has had all the THC removed. Lazarus Naturals does not currently produce any broad spectrum CBD products.

Isolated Extracts, or Isolate

Isolated extracts are one step past broad-spectrum extracts. To produce an isolated cannabinoid, additional filtration steps are used to remove all cannabinoid and terpene content except for a single, targeted cannabinoid (such as CBD). CBD isolate, for instance, is a pure CBD product where all other cannabinoids have been removed from the formulation. This product is ideal for individuals who are sensitive to THC or who want to be sure to avoid ingesting it. Using a CBD isolate product will not result in intoxication, but even when CBD isolate products are certified THC-free by a reputable laboratory, it's possible that a drug screening could still flag CBD as a cannabis compound.

An Overview of Cannabinoid Pharmacokinetics

Absorption, distribution, and metabolism determine the onset and duration of effect for different modes of cannabinoid administration. Absorption refers to the amount of active

cannabinoids that have made it into your blood system (in the liquid “plasma” part of the blood). More colloquially, absorption sometimes refers to the concentration of cannabinoids taking effect beneath the skin, as in the case of topical administrations. This “active” amount after oral administration can be reduced by metabolic processes in the body such as digestion.

Factors such as the concentration of active cannabinoids in your body, their distribution, and how long they remain in the body are affected by product formulation, delivery method, and physiological differences between individuals. For topical or oral administration, studies have shown that absorption can be enhanced by administering cannabinoids with fats (e.g., coconut oil or olive oil).

Delivery Methods, or Routes of Administration

Combustion and Vaporization

Combustion (smoking) and **vaporization** are the most common routes of administration for recreational cannabis but are not recommended for medical use because of the high degree of variability in doses. Factors such as depth of inhalation, duration of breath-holding, temperature of the vaporizer, and potency of the cannabis can all affect absorption and therefore make it difficult to get a consistent dose time after time. Inhalation, whether through smoking or vaporizing, can cause damage to the respiratory system due to the production of toxic byproducts involved in either method.

Oromucosal and Oral Administration

Oromucosal and **oral** administration are popular delivery methods due to their convenience. They have the added benefit of accurate and consistent dosing. Oromucosal

administration involves the absorption of cannabinoids through the various mucous membranes that line the inside of the mouth. Sublingual (meaning "under the tongue") administration is popular because it is easy to hold cannabinoid oil there for a few minutes for maximal absorption. Oral ingestion of cannabinoids in the form of edibles or soft gels is by far the most convenient mode of administration but the cannabinoids do go through metabolization by the digestive tract. This "first-pass metabolism" decreases the concentration of cannabinoids that are available to enter the bloodstream. Even so, oromucosal and oral preparations of cannabis are highly recommended for chronic conditions and symptoms.

Topical Administration

Topical administration is ideal for targeting localized symptoms, such as those related to arthritis or other types of focal pain. Topicals include lotion or gel formulations that include permeation enhancers to help the cannabinoids pass through the skin. Topicals can also be in patch form, which results in a steady dose of cannabinoids being delivered over a prolonged period of time to one area.

Other Delivery Methods

Other routes of administration include **suppositories**, which take advantage of the permeability of membrane linings in the same way oromucosal delivery does. This delivery method can be appropriate for specific patient populations such as people dealing with cancer or symptoms affecting the gastrointestinal tract[23].

[23] MacCallum, C.A., & Russo, E.B. (2018). Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*, *49*, 12–19. https://doi.org/10.1016/j.ejim.2018.01.004

Practical Considerations for Use

While there are ranges that can be recommended based on body weight and symptom severity, cannabinoid administration is best determined on an individual basis because each individual has a unique combination of specific physical, genetic, and metabolic characteristics. The prevailing guidance is that individuals should *start low and go slow* when incorporating THC into their lives, but this advice ***does not*** apply to CBD. Here are reasons why:

1) CBD's psychotropic effects are non-intoxicating.
2) It's well-documented that not only does CBD require larger serving sizes but that high doses are much better tolerated than those of THC. Seizure disorders, for example, are treated with between 25 and 50 mg/kg CBD, which equates to 4,500 mg of CBD for a 200-pound person[30].

Symptom Intensity	Body Weight, pounds (lb)			
	50–100 lb	100–150 lb	150–200 lb	200+ lb
1 – Mild	10–25 mg	20–40 mg	25–50 mg	40–75 mg
2 – Moderate	25–50 mg	40–75 mg	50–100 mg	75–150 mg
3 – Severe	50–100 mg	75–150 mg	100–200 mg	150–250 mg

If a CBD product is not producing the desired effects, a person can try taking that same serving size with or without food. For some people, CBD on an empty stomach results in a more pronounced effect. Many studies, though, show that CBD exerts its effects more powerfully when co-administered with fats, so taking CBD with fatty foods or soon after eating could be beneficial in boosting CBD's effects.

The Research Environment

Decades of cannabis prohibition in the United States at the federal and state levels have made it extremely difficult for all but a few researchers to obtain the federal permit required to conduct laboratory research with cannabis and its myriad compounds. This lack of access has significantly hindered scientific progress into the investigation of cannabis. Progress is finally being made in terms of a broadening of approved sources of cannabis for federally funded research for the first time in more than 50 years (a cultivar from 1968 grown at the University of Mississippi was previously the only source[24]).

Many state prohibitions are being repealed for both medical cannabis and recreational cannabis, and the federal government has stated its intention not to pursue marijuana criminalization in states that have removed the bans. Cannabis products and therapies are undergoing more clinical and laboratory research to determine the mechanics of the active components and to explore, validate, and translate the therapeutic potential of cannabinoids. Though THC takes a big portion of the research attention, CBD's recognized potential in recent years has made it of particular interest to researchers.

The changing social and political landscape surrounding cannabis's effects is leading to a more straightforward and accessible regulatory path for well-designed and properly conducted studies of CBD. Though scientists have been able to identify CBD's ability to reduce seizures and relieve muscle spasticity and pain, there is still a need to understand the molecular targets and interactions that are making such outcomes possible. The potential for further clinical

[24] Gurman, S. (2021, May 14). Marijuana medical research growers receive U.S. approval. *The Wall Street Journal*. https://www.wsj.com/articles/marijuana-research-growers-receive-u-s-approval-11621024843

development of CBD-based and CBD-derived therapies is vast, and industries across disciplines are getting on board.