What are Cannabinoids and How Do They Work?

Cannabinoids are a class of compounds that were first discovered in cannabis plants but have since been identified as naturally occurring in many vertebrate animals. Cannabinoids include phytocannabinoids such as THC and CBD, endocannabinoids which are an intrinsic part of the body's signaling systems, and cannabinoids synthesized by scientists (such as the FDA-approved drug dronabinol) which are used to treat a number of disease conditions.

There are several metabolic factors that can influence onset times, absorption rates, duration of effects, and the time a cannabinoid such as CBD takes to reach its maximum concentration in the bloodstream. Variations in product formulations, as well as individuals, though, can result in variable effects—thus, two different people can take the same amount of the same product and have different results . An individual's response is affected by factors such as history of cannabis use, genetics, body size, and composition and distribution of fat, as well as one's health status, diet, microbiome, and individual differences in metabolism and liver function.

Factors in Delivery Methods of Cannabinoids

Onset

Onset is when an individual begins to feel the effects of a compound. In general, oromucosal administration has faster onset times than oral administration. Onset times for topical administration are more difficult to measure because of the variability of product formulations,

but the range of onset times is closer to that of oral administration than oromucosal administration.

For most people, sublingual administration has the fastest range of onset times, followed by topical, then oral administration[1,2,3,4].

Duration

Duration describes how long the effects of a compound last. Notably, the effects of a compound might subside before the compound itself is eliminated completely from one's body. This phenomenon is because the lipophilic properties of cannabinoids cause them to be readily stored in adipose tissues throughout the body and continually released over time into the surrounding areas. Long-term use of cannabinoids increases the amount of time it takes before CBD is no longer detectable in your body.

Topical administration tends to result in the longest duration, followed by oral and oromucosal administration, which have similar ranges. Because metabolic factors differ from person to person, the range of duration times for each of these delivery methods can overlap. While concentrations of CBD delivered through sublingual or topical administration gradually

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[1] Narang, N., & Sharma, J. (2011). Sublingual mucosa as a route for systemic drug delivery. *International Journal of Pharmacy and Pharmaceutical Sciences*, (3), 18–22.

[2] Valiveti, S., Hammell, D. C., Earles, D. C., & Stinchcomb, A. L. (2004). In vitro/in vivo correlation studies for transdermal delta 8-THC development. *Journal of pharmaceutical sciences*, *93*(5), 1154–1164. https://doi.org/10.1002/jps.20036

[3] Nadulski, T., Sporkert, F., Schnelle, M., Stadelmann, A. M., Roser, P., Schefter, T., & Pragst, F. (2005). Simultaneous and sensitive analysis of THC, 11-OH-THC, THC-COOH, CBD, and CBN by GC-MS in plasma after oral application of small doses of THC and cannabis extract. *Journal of analytical toxicology*, *29*(8), 782–789. https://doi.org/10.1093/jat/29.8.782

[4] 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

decrease after reaching their peaks, oral administration of CBD results in a second peak in concentration that extends the duration of effects[4,5,6].

Bioavailability

Bioavailability is the amount of an active compound that is distributed throughout the body following administration. Bioavailability is sometimes referred to as absorption, and even scientists are in contention over how the terminology should be correctly used[7].

There are very few clinical studies on the bioavailability of CBD, but based on what is known of THC pharmacokinetics combined with the limited number of studies that have been performed in animals and humans, sublingual and oral administration are reported to have comparable bioavailability ranges. Oromucosal administration is expected to exhibit slightly better bioavailability because this route mainly avoids the digestive tract and resulting metabolism, unlike orally administered CBD.

For transdermal administration, there have been no published studies on bioavailability rates so far, but it is known that CBD is 10 times more permeable across human skin than THC is[8].

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[5] Agurell, S., Carlsson, S., Lindgren, J. E., Ohlsson, A., Gillespie, H., & Hollister, L. (1981). Interactions of delta 1-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. *Experientia*, *37*(10), 1090–1092. https://doi.org/10.1007/BF02085029

[6] Grotenhermen F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical pharmacokinetics*, *42*(4), 327–360. https://doi.org/10.2165/00003088-200342040-00003

[7] Chiou W. L. (2001). The rate and extent of oral bioavailability versus the rate and extent of oral absorption: clarification and recommendation of terminology. *Journal of pharmacokinetics and pharmacodynamics*, *28*(1), 3–6. https://doi.org/10.1023/a:1011544501243

[8] Challapalli, P. V., & Stinchcomb, A. L. (2002). In vitro experiment optimization for measuring tetrahydrocannabinol skin permeation. *International journal of pharmaceutics*, *241*(2), 329–339. https://doi.org/10.1016/s0378-5173(02)00262-4

Co-administration with fats has been shown to increase cannabinoid bioavailability[9]. Absorption rates increase when CBD is taken with food or when it is taken in the form of softgels, which include lipids such as oil to increase absorption.

Different Ways to Administer Cannabinoids

Oromucosal administration (a.k.a. intraoral administration)

Oromucosal administration refers to the absorption of a substance through any of the mucosal linings on the inside of the mouth. Regions inside the mouth are often divided into ***sublingual*** (under the tongue) and ***buccal*** (pronounced "buckle" and referring to the rest of the oral cavity such as the cheeks and roof of the mouth). The skin (or more technically, the epithelial lining) of the mouth is highly vascularized, meaning that there are many small blood vessels running directly under the skin. Oral administration takes advantage of the high permeability of the mucous membranes in the mouth.

Sublingual administration is the recommended location for cannabinoid tinctures because it allows the individual to easily hold the product and delay swallowing for 30-60 seconds for maximal absorption. (A small portion of oromucosally administered cannabinoid product is nearly always swallowed and subsequently undergoes the slower administration method of oral

[9] Stott, C. G., White, L., Wright, S., Wilbraham, D., & Guy, G. W. (2013). A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. *European journal of clinical pharmacology*, *69*(5), 1135–1147. https://doi.org/10.1007/s00228-012-1441-0

delivery.) Individuals may also "swish" a tincture for 30 seconds before swallowing, but some individuals prefer not to taste the tincture or experience the viscous texture of the liquid.

The onset of effects is between 15 and 45 minutes, with maximum concentration reached in a matter of minutes[4]. Studies have indicated a range of 9-23% bioavailability[10] and a duration of effects that lasts 4-12 hours, with effects gradually lessening over time.

Administration of cannabis through the oral mucous membrane is an extraordinarily fast and direct method of cannabis delivery. This method effectively transports cannabinoids across the mucous membranes and into the bloodstream for circulation to the brain, where cannabinoids activate receptors to effect physiological changes. The direct nature of absorption allows for the administration of precise and metered doses in a delivery method that is acceptable for most people.

Oral administration

Cannabinoids administered orally have been reported to have onset times between 60 and 180 minutes and last approximately 6-8 hours. The convenience of orally administered cannabinoids makes them ideal for management of chronic disease and or symptoms, but the delayed onset time can make titration of serving size difficult. Pharmacokinetic studies have

[10] Mannila, J., Järvinen, T., Järvinen, K., Tervonen, J., & Jarho, P. (2006). Sublingual administration of Delta9-tetrahydrocannabinol/beta-cyclodextrin complex increases the bioavailability of Delta9-tetrahydrocannabinol in rabbits. *Life sciences*, *78*(17), 1911–1914. https://doi.org/10.1016/j.lfs.2005.08.025

reported that orally administered cannabinoids reach their maximum concentration in the bloodstream at around 2 hours, with absorption rates reported between 6 and 20%[11,12].

Oral administration has a reduced bioavailability and delayed onset time compared with other delivery methods such as oromucosal or inhaled administration because the cannabinoids have to first traverse the digestive tract; this "first-pass metabolism" means the cannabinoid formulation is metabolized by the liver, which reduces the concentration of active cannabinoids that enter the bloodstream for distribution throughout the body.

While digestion by the liver does delay relative onset times and reduce bioavailability, it is also responsible for *enterohepatic circulation*, a process where a portion of the cannabinoids are transported back to the liver for secondary metabolism and subsequent redistribution. This biological process leads to a second peak in plasma concentration that extends the duration of effects for orally administered cannabis.

Eating or drinking cannabis products, such as in a tincture, food or beverage product, or in a capsule is a way to consistently control the amount of THC and CBD (or whatever combination of cannabinoids one desires) that is consumed (because the ingestible product can be manufactured in a systematic, consistent, and measured way). Because the onset of activity is more delayed than in the more immediate response of inhaled cannabis, choosing edible and potable cannabis products can be a good option for people who are managing a more chronic condition.

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[11] Mechoulam, R., Parker, L. A., & Gallily, R. (2002). Cannabidiol: an overview of some pharmacological aspects. *Journal of clinical pharmacology*, *42*(S1), 11S–19S. https://doi.org/10.1002/j.1552-4604.2002.tb05998.x

[12] Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., & Perez-Reyes, M. (1983). Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clinical pharmacology and therapeutics*, *34*(3), 352–363. https://doi.org/10.1038/clpt.1983.179

Somewhere in between: Nanoemulsions

Nanoemulsions are increasing being used in the food industry because they can encapsulate bioactive compounds. In the cannabis industry, nanoemulsions are used to produce tiny, stable parcels of cannabinoids that are encapsulated in droplets that make them more resistant to the body's metabolic processes and thereby increases overall bioavailability and therapeutic potential of the cannabinoids. In general, nanomedicine delivery systems are nontoxic, biodegradable, and do not activate an immune response, but it's not yet clear by how much nanoemulsion delivery improves bioavailability. A study in rats noted a 65% increase in bioavailability when rats were administered a CBD nanoemulsion versus pure CBD oil; while it's been noted that the metabolism of CBD is different in rats and humans, the researchers still expected a huge increase in bioavailability for nanoemulsified CBD administered to humans[13,14].

Topical administration (a.k.a. transdermal administration)

Transdermal delivery describes absorption of a substance through the skin via patches or other formulations applied directly to the skin. Sometimes the more general term ***topical administration*** is used to differentiate gel- or lotion-like formulations from skin patches. Patches have the advantage of being specifically packaged to deliver a certain dose over a predetermined amount of time. Self-applied formulations such as cannabinoid-infused gels, lotions, and oils are more variable.

Because topicals can be applied directly to the area of discomfort, this delivery method is highly beneficial for localized pain relief, muscle soreness, tension, and inflammation rather than

[13] Gupta, A., Eral, H. B., Hatton, T. A., & Doyle, P. S. (2016). Nanoemulsions: formation, properties and applications. *Soft matter*, *12*(11), 2826–2841. https://doi.org/10.1039/c5sm02958a

[14] Aqil, F., Munagala, R., Jeyabalan, J., & Vadhanam, M. V. (2013). Bioavailability of phytochemicals and its enhancement by drug delivery systems. *Cancer letters*, *334*(1), 133–141. https://doi.org/10.1016/j.canlet.2013.02.032

a more distributed, systemic effect. Transdermal delivery also allows for prolonged delivery of an active treatment compound over time. With inhalation, ingestion, and intraoral delivery methods, the concentration of cannabinoids in the blood rises, peaks, then dips. Transdermal methods can deliver a more consistent level of cannabinoids, with levels decreasing steadily over time. Due to variability of product formulations, topically administered cannabinoids exhibit variable bioavailability. More studies are needed to better understand the mechanics of transdermal cannabinoid transport.

Another advantage of transdermal delivery is how well-tolerated it is across a variety of medical conditions. Most people who turn to a transdermal application are those who are trying to manage long-term chronic pain. When pain can be managed in large part by transdermal cannabinoids, healthcare providers can sometimes reduce treatment complexity and number of prescriptions, which in turn has the added benefit of often increasing ease of following the treatment plan.

Pulmonary Administration (a.k.a. Inhalation, or Smoking and Vaporization)

Smoking

Combustion is a term that describes when the cured cannabis plant is lit on fire and the smoke is inhaled. Combustion occurs at temperatures of 230° C (446° F) and above, essentially the temperature that dried cannabis flowers and hash products reach when burned and smoked. Though combustion is a great way to decarboxylate cannabis (a chemical breakdown process), thus releasing the active cannabinoids and terpenes, it also releases associated smoke toxins that are highly undesirable. These toxic inhalants include known carcinogens such as benzene, carbon

monoxide, toluene, naphthalene, acetaldehyde, phenol, and hydrogen cyanide at levels comparable to inhalation of tobacco smoke[15]. These known byproducts of combustion are thought to be a major culprit in smoking-related cancers and can at the very least pose respiratory hazards. Interestingly, though, cannabis smokers do not seem to have increased risk for lung or oral cancers; scientists hypothesize that there are protective effects of cannabis that counterbalance the harmful effects of the combustion byproducts[16].

Vaporizing

Vaporizers heat cannabis to a temperature at which active cannabinoids are released (i.e., the temperature point of *decarboxylation*) but aim to keep the temperature below the temperature threshold of combustion, the point at which smoke is formed (at 266°-446° F or 190°-200° C). Vaporizing avoids most of the smoke and toxins associated with combustion (smoking) and thus can decrease the respiratory symptoms that are associated with long-term inhalation of combusted cannabis. It should be noted that the short-term effects of smoking cannabis do not seem to worry physicians; the health consequences produced from inhalation of combusted smoke develop primarily following chronic use[17,18,19].

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[15] Gieringer, D. H. (2001). Cannabis vaporization: A promising strategy for smoke harm reduction. *Journal of Cannabis Therapeutics*, *1*(3), 153–170. https://doi.org/10.1300/J175v01n03_10

[16] Jett, J., Stone, E., Warren, G., & Cummings, K. M. (2018). Cannabis Use, Lung Cancer, and Related Issues. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*, *13*(4), 480–487. https://doi.org/10.1016/j.jtho.2017.12.013

[17] Tashkin, D. P., Baldwin, G. C., Sarafian, T., Dubinett, S., & Roth, M. D. (2002). Respiratory and immunologic consequences of marijuana smoking. *Journal of clinical pharmacology*, *42*(S1), 71S–81S. https://doi.org/10.1002/j.1552-4604.2002.tb06006.x

[18] Abrams, D. I., Vizoso, H. P., Shade, S. B., Jay, C., Kelly, M. E., & Benowitz, N. L. (2007). Vaporization as a smokeless cannabis delivery system: a pilot study. *Clinical pharmacology and therapeutics*, *82*(5), 572–578. https://doi.org/10.1038/sj.clpt.6100200

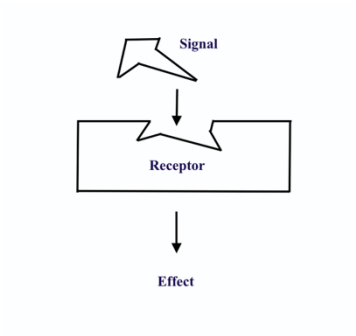
[19] Earleywine, M., & Barnwell, S. S. (2007). Decreased respiratory symptoms in cannabis users who vaporize. *Harm reduction journal*, *4*, 11. https://doi.org/10.1186/1477-7517-4-11

Smoking and vaporization are not the recommended methods of therapeutic administration of cannabis because of the risks associated with the toxic byproducts produced as well as the difficulty in precise dosing. Not only is 30-50% of cannabis lost to "side-stream" smoke that is not inhaled, but the bioavailability of inhaled cannabis is largely dependent on varying factors such as depth of inhalation, duration, and volume of smoke, which can differ significantly from person to person and from session to session[20].

The Molecular Mechanics of Cannabinoid Action

How Cannabinoids Work: The Ligand-Receptor Relationship

Processes in the body are mediated by molecules interacting; these interactions are mediated by molecules binding to each other (one major class of molecules interacts with others in a way often described as a lock and key, for example). In the endocannabinoid receptor system (and other biological systems like it), interactions involve *ligand–receptor* mechanics. A *ligand* (the key) is a molecule that can bind proteins designed to detect them, which is called a *receptor* (the lock).



[20] Gieringer, D., St. Laurent, J., & Goodrich, S. (2004). Cannabis vaporizer combines efficient delivery of thc with effective suppression of pyrolytic compounds. *Journal of Cannabis Therapeutics*, *4*(1), 7–27. https://doi.org/10.1300/j175v04n01_02

The binding of ligands to their specific receptors is how cells gather information about and respond to their environments. Based on the sequence of molecular and cellular events that happens after ligand–receptor binding, our bodies can change or maintain the state they're in.

Every receptor has a binding site of a specific shape and structure that determines what molecule can bind to it. Some receptor proteins are highly selective—their binding sites are shaped to fit only a highly specific set of ligands—but the vast majority of receptors have binding sites that are more general and can fit a number of possible ligands. Some ligands bind strongly, whereas others come and go more easily.

Different types of binding lead to different effects

When a ligand binds to the main (*orthostatic*) site of a receptor, it can act as an agonist or as an antagonist. An *agonist* triggers a physiological response, whereas an *antagonist* binds to the receptor and blocks any response. As a consequence, antagonists prevent other potential agonists from binding the receptor and triggering a response. In this way, ligands compete with one another for available binding sites on the receptors they can fit into.

Another kind of ligand–receptor binding involves *allosteric sites*, which are locations on the receptor that don't trigger the receptor's usual cascade of effects but instead change the shape of the receptor itself and thereby change the shape of the binding site. Allosteric modulators can be described as positive, neutral, or negative: positive allosteric modulators make it easier for certain ligands to bind, neutral modulators do not affect the orthostatic site, and negative modulators block (or significantly decrease) the ability of the usual ligands to bind.

Scientists, once they understand the specific receptor proteins and what endogenous or exogenous ligands bind to that receptor, can harness the specificity of a ligand–receptor system

to affect desired outcomes. For instance, they can develop a drug that binds to a specific receptor type so tightly that ligands that usually bind there cannot, thus blocking its usual function; this is how some antipsychotic drugs work.

Part of Us: The Endocannabinoid System

The endocannabinoid system is widely distributed throughout the brain and spinal cord and plays a prominent role in the regulation of many physiological processes including inflammation, appetite regulation, metabolism, thermogenesis, immune response, cardiovascular function, digestion, synaptic plasticity, pain, memory, movement, sleep/wake cycles, regulation of stress and emotion, and digestion[21,22,23].

The cannabinoid receptors and the endocannabinoids

The ECS consists of the two cannabinoid receptors CB1 and CB2, the endocannabinoids AEA (also known as anandamide and N-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol), and the enzymes that break those endocannabinoids down: FAAH (fatty acid amide hydrolase) and MAG lipase (monoacylglycerol lipase)[24]. AEA is the predominant player in the ECS.

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[21] Aggarwal S. K. (2013). Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *The Clinical journal of pain*, *29*(2), 162–171. https://doi.org/10.1097/AJP.0b013e31824c5e4c

[22] Rodríguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F. J., Bilbao, A., Cippitelli, A., & Navarro, M. (2005). The endocannabinoid system: physiology and pharmacology. *Alcohol and alcoholism (Oxford, Oxfordshire)*, *40*(1), 2–14. https://doi.org/10.1093/alcalc/agh110

[23] Greco, R., Gasperi, V., Maccarrone, M., & Tassorelli, C. (2010). The endocannabinoid system and migraine. *Experimental neurology*, *224*(1), 85–91. https://doi.org/10.1016/j.expneurol.2010.03.029

[24] Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., & Mechoulam, R. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science (New York, N.Y.)*, *258*(5090), 1946–1949. https://doi.org/10.1126/science.1470919

Aside from releasing FAAH or MAG lipase to move through the cellular spaces and degrade unbound endocannabinoids, the ECS also regulates reuptake, a process where cells reabsorb transmitters for future re-release. These reuptake systems take AEA away from the intercellular space where they interact with the cannabinoid receptors. In short, enzyme degradation and reuptake both reduce the concentration of active endocannabinoids in the body[25].

CBD has low binding affinity at the orthostatic sites of the CB1 and CB2 receptors, so it's likely that CBD exerts its physiological effects through more indirect pathways. This is in contrast to THC, for instance, which directly activates the ECS by binding to the CB1 and CB2 receptors. CBD is known to be a negative allosteric inhibitor of the CB1 receptor—meaning that once CBD has bound to the receptor, the CB1 receptor's orthostatic site changes, making it difficult for the agonist THC to bind and activate the signal cascade.

CBD is also known to reduce the amount of FAAH in the body, consequently increasing AEA levels and leading to an increase in the positive effects that result from activation of the ECS. Similarly, CBD also affects the cellular systems that are responsible for the AEA reuptake process. CBD reduces the activity of reuptake systems, allowing for more AEA to continue circulating, binding, and activating the cannabinoid receptors.

Indirect effects on other neurotransmitter receptor signaling systems such as the serotonin, NMDA, opiate, and GABA ligand-receptors allow endocannabinoids to modulate other networks outside of the ECS.

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[25] Howlett, A. C., Barth, F., Bonner, T. I., Cabral, G., Casellas, P., Devane, W. A., Felder, C. C., Herkenham, M., Mackie, K., Martin, B. R., Mechoulam, R., & Pertwee, R. G. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacological reviews*, *54*(2), 161–202. https://doi.org/10.1124/pr.54.2.161

The molecular mechanisms that underlie the effects of cannabinoids on the mind and body are still being explored. Scientists and clinicians are endeavoring towards improved understanding of the function, mechanics, and chemistry of cannabinoids: basic research is being conducted in laboratory and animal models to elucidate the pathways that involve cannabinoids, setting the foundation for rigorous clinical and translational studies.