# Research Findings Relating to the Pharmacokinetics and Pharmacodynamics of Cannabidiol (CBD)

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This article is based upon published scientific findings.
However, the information provided in this article does not constitute medical advice.

The most abundant cannabinoid belonging to plants of the *cannabis* genus is the psychoactive compound delta-9-tetrahydrocannabinol (THC), which is responsible for most of the adverse effects relating to cannabis use. In contrast, Lucas, Galettis, and Schneider (2018) note that cannabidiol (CBD) is a non-psychoactive cannabinoid "reported to have analgesic, neuroprotective, anticonvulsant, antiemetic, antispasmodic and anti-inflammatory properties" (p. 2477). A review of the literature shows that CBD offers a number of beneficial pharmacological effects. At higher serving sizes, it has been used to address a broad variety of conditions ranging from schizophrenia and dementia to diabetes and nausea. At lower serving sizes, it is used for preventative health purposes as an antioxidant, anti-inflammatory and/or neuroprotective agent (Iffland & Grotenhermen, 2017).

## Absorption

The pharmacokinetics or movement of CBD through the body is dependent on the preparation of the product and the method of administration. Absorbing CBD through inhalation, via oromucosal methods and/or transdermally (through topical application) all avoid first-pass metabolism by the liver.

Inhaled CBD enters capillaries in the lungs, passes through into the bloodstream and quickly crosses the blood-brain barrier with peak plasma concentrations reached within 3-10 minutes. Additionally, inhalation results in maximum plasma concentrations that are higher compared to oromucosal or oral ingestion methods. Inhaled CBD has an approximate systemic bioavailability of 31% (the fraction of CBD estimated to reach the bloodstream). Although smoking is known to carry many risks, vaporizing CBD does not hold the same "respiratory risk

associated with smoking cannabis" as the toxic compounds formed with combustion are avoided (Lucas et al., 2018, p. 2478).

Oromucosal delivery of CBD also results in fast absorption and therefore, can provide rapid symptom relief. Oromucosal absorption can be achieved through the sublingual or buccal mucosa. Sublingual administration involves placing the CBD beneath the tongue to allow for absorption through the mucosa and directly into the bloodstream. Buccal administration is achieved when the CBD is placed between the gums and cheek, where it is absorbed through the mucosa and directly enters systemic circulation. Both forms of oromucosal delivery achieve higher plasma concentrations compared to immediate oral delivery but lower concentrations relative to inhalation. After the CBD is held sublingually or buccally for a period of time and then swallowed, oral absorption will still occur (Lucas et al., 2018).

When CBD is ingested orally, either in oil form that is immediately swallowed or in the form of gel capsules, it moves through the digestive system and undergoes extensive hepatic first-pass metabolism. Mehvar (2018) explains that the "first-pass effect" occurs after oral administration of a drug moves through the gastrointestinal tract and passes through the liver prior to reaching the bloodstream (p. 92). This means that the oral bioavailability of CBD is limited due to incomplete absorption through metabolism and degradation by the liver. In summary, oral administration results in a lower peak plasma concentration, with a longer delay to reach peak plasma concentration, when compared with inhalational or oromucosal delivery methods. Lucas et al., (2018) explain that CBD is highly lipophilic and therefore, has poor oral bioavailability, "estimated to be as low as 6%" (p. 2478). Hence, the fraction of CBD that reaches systemic circulation through oral administration is considerably low. This highlights the fact that oral delivery methods in the form of gel capsules or immediately swallowing CBD oil results in larger servings of CBD to achieve desired effect. As CBD serving size increases, so do the financial implications and the potential for undesirable side-effects.

## Distribution

Once CBD is ingested and absorbed, it is rapidly distributed to highly vascular organs such as the lungs, heart, brain and liver and then it circulates to other parts of the body. Lucas et al., (2018) highlight that distribution of cannabinoids throughout the body "may be affected by body size and composition and disease states influencing permeability of blood-tissue barriers." (p. 2478). CBD is considered lipophilic, which means it has the ability to dissolve or attach to lipids. It is this lipophilicity that allows CBD to pass the blood-brain barrier (Maroon & Bost, 2018). Additionally, the lipophilic nature of cannabinoids gives them the propensity to accumulate in adipose tissue and therefore, the potential exists for cannabinoid activity weeks after administration (Lucas et al., 2018).

## Metabolism: Cytochrome P450-Complex Enzymes

With all of the promising research into CBD, it is predicted that this cannabinoid will soon be widely available in a multitude of preparations: pharmaceutical, nutraceutical and herbal. As a result of its increased use and growing popularity, a responsible explanation into the potential for CBD-drug interactions is needed to ensure its safe and effective use.

CBD is metabolized by the hepatic cytochrome P450 enzyme system (P450-complex). This family of liver enzymes is also responsible for the metabolism of many different drugs that fill our pharmacy shelves. As a result, the administration of CBD with other drugs holds the potential for CBD-drug interactions. One of the enzymes belonging to the P450-complex is CYP3A4, which is partly responsible for the metabolism of CBD and "approximately 60% of clinically prescribed drugs" on the market (Iffland & Grotenhermen, 2017, p. 141). As a result, "the potential exists for pharmacokinetic interactions between… CBD and other drugs, via inhibition or induction of enzymes or transporters and additionally, pharmacodynamic drug-drug interactions" may occur (Lucas et al., 2018, p. 2479).

Why is this important to relay to anybody using CBD in combination with other prescribed or over-the-counter medication? Research shows that CBD dominates the P450

enzyme system and acts to displace chemical competitors, thereby inhibiting the liver enzymes from fully metabolizing other compounds. The serving size of CBD consumed as well as the individual's unique metabolism will determine the duration of time that CBD will exert dominance over the P450 enzymes. The concomitant use of CBD and other medications could render the pharmaceuticals less or more effective and may require dosing adjustments (Stott, White, Wright, Wilbraham & Guy, 2013).

What does this mean for CBD consumers? Research shows that the partial or incomplete metabolism of medications used concomitantly with CBD can result in an altered pharmacological effect and the potential for adverse effects. This knowledge together with an emphasis that people should keep close communication with their doctors about CBD use will help enable close monitoring and the adjustment of an individual's prescription medication regimen early enough to ensure a more optimal response with minimal, if any, adverse effects (Stott et al., 2013).

A 2013 study investigated the potential for drug-drug interactions when Sativex, an oromucosal spray, was used in combination with other medications known to induce or inhibit the P450 enzyme system. Sativex contains a 1:1 ratio of THC to CBD and it is prescribed to multiple sclerosis patients; therefore, there is a high likelihood that multiple drugs will be used in combination with the THC/CBD spray. The authors of this study stated that the inhibitory effect of CBD on the P450 enzymes will only occur when high concentrations of CBD are consumed. Specifically, "in normal dosing, peak plasma concentrations of CBD are… 400-fold lower than the levels at which [P450-complex enzyme] inhibition may be anticipated" (Stott et al., 2013, p. 2). In summary, the THC/CBD spray was well tolerated by study participants when taken in combination with the antibiotic rifampicin, the synthetic antifungal ketoconazole and the proton-pump inhibitor omeprazole (Stott et al., 2013).

## Elimination

CBD has a long elimination half-life. Lucas, Galettis, & Schneider (2018) note that after inhalation, the average half-life is reached at approximately 35 hours. After repeated daily oral administration, the elimination half-life ranged from “2 to 5 days” (p. 2479).

## Safety Profile of CBD

A recent safety and side effect review of both animal and human studies described CBD to have an excellent safety profile at a wide range of serving sizes. The most common side effects detailed in the studies reviewed were appetite changes, tiredness and diarrhea. Studies that detail the effects of CBD in comparison to other prescription and over-the-counter drugs used to treat a variety of conditions, found that CBD had a favorable side effect profile (Iffland & Grotenhermen, 2017). In 2011, a review of 132 published studies sought to address the safety and side effect profile of CBD. The review highlighted both *in vivo* and *in vitro* studies that focused on the administration of a wide range of CBD concentrations. The authors noted that CBD does not hold the potential to alter physiological parameters such as heart rate, blood pressure and body temperature. Several studies reviewed suggested that CBD has no negative influence on food intake, gastrointestinal transit, psychomotor or psychological functions. The chronic use of CBD and high serving sizes up to 1,500 mg/day have been shown to be well tolerated by humans. Some studies highlighted that CBD can alter hepatic drug metabolism and holds the potential to decrease the activities of p-glycoprotein drug transporters (Bergamaschi, Queiroz, Zuardi & Crippa, 2011). Much of the research into CBD “suggests that it has no addictive effects, [a] good safety profile and has exhibited powerful therapeutic potential in several vital areas” (Noreen, Muhammad, Akhtar, Azam, & Anwar, 2018, para. 1). Recently, the World Anti-Doping Agency (2018) officially stated that CBD will no longer appear on the list of banned substances for international sport competition for 2018 (p. 8).

## CBD-Drug Interactions

Despite the fact that CBD is a safe, non-intoxicating compound that holds no potential for addiction, the potential for CBD-drug interactions do exist. Below are some research findings relating to a few medications that can be influenced when used in combination with CBD due to the cannabinoids action on the cytochrome P450 enzyme system. The information below is a representation of the types of interactions noted in the research and is far from a complete list of the drugs that can be affected by the concomitant use of CBD.

### Fentanyl

According to the National Institute on Drug Abuse, more than 115 people succumb to opioid overdose in the United States every day. Opioid addiction has reached crisis proportions and it is now considered a national public health crisis (para. 1).

Ren et al., (as cited in Manini et al., 2015) conducted preclinical research with findings that suggest CBD may offer therapeutic effects for opioid abuse. The study showed that "CBD can inhibit reinstatement of heroin-seeking behavior" (p. 2). The researchers noted that the administration of CBD continued to have an inhibiting effect on drug seeking behaviors two weeks post administration.

Another animal study published by Katsidoni, Anagnostou and Panagis (2013) reinforced these findings and concluded that CBD acts to interfere with brain reward pathways and may be helpful in "reducing the rewarding effect of opioids" (para. 1).

A study conducted by Manini et al., (2015) sought to determine "the safety and pharmacokinetics of CBD when administered concomitantly with [intravenous fentanyl]" in human subjects (p. 3). Findings showed that CBD was well tolerated at serving sizes of 800mg per day when taken concomitantly with fentanyl and that it did not act to exacerbate the adverse effects of fentanyl on the human body. In summary, the use of CBD together with drugs classified as opioids is "safe and well tolerated" (Manini et al., 2015, p. 9).

These findings are significant as they create the groundwork needed for future research to determine the extent of CBD's beneficial impact on opioid cravings and dependence in humans.

Warfarin

The fact that CBD shares the same enzymatic pathways as the prescription blood-thinner warfarin, warrants further explanation. A case report published in 2018, looked into the effects experienced by a patient undergoing warfarin therapy after introducing CBD. Warfarin is a widely prescribed anticoagulant that has a narrow therapeutic range. Individuals require frequent monitoring of their International Normalized Ratio (INR) to achieve and maintain the drug's necessary effects. Like CBD, warfarin is metabolized by the cytochrome P450 enzyme system. For six months prior to the commencement of the study, the patient's INR had been within normal range. The patient was placed on a total daily serving of 5mg/kg/day CBD. This serving was titrated upward in increments of 5mg/kg/day every two weeks. This translated to an initial daily serving of 530mg CBD, and after 17 months of increasing his CBD serving, he was taking 3604mg CBD per day. These are very high daily servings of CBD and far from the average seen in most studies reviewed. During the study period, the patient had a rise in INR values and the attending primary care physician reduced his warfarin dose by approximately 30% to keep him within therapeutic range. An increase in INR's suggests that when CBD is used concurrently with warfarin, it acts to inhibit the P450-complex enzyme system. The inhibition of these liver enzymes impairs the metabolism of the blood thinner, thereby prolonging the drugs activity and increasing its effect. The researchers concluded that patients taking warfarin should have their INR values closely monitored when taking CBD and adjust warfarin dosages as recommended by their doctor. It is important to note that with close INR monitoring and warfarin dosage adjustments, the patient had no bleeding complications throughout the study period (Grayson, Vines, Nichol, & Szaflarski, 2018, p. 10-11).

Clobazam

Approximately one third of people with epilepsy are said to have uncontrolled drug resistant epilepsy with refractory seizures. People with refractory epilepsy have seizures that are frequent and severe without adequate control from available seizure medications. For this patient population, quality of life is severely impacted. Therefore, a great need exists for the exploration of additional treatment options. Research shows that CBD could provide an alternative for those with refractory seizures. A recent study investigated the potential drug-drug interactions between Clobazam and CBD in children with refractory epilepsy. The authors noted that "CBD might have safe and effective antiepileptic properties comparable to U.S. Food and Drug Administration FDA-approved antiepileptic drugs" (Geffrey, Pollack, Bruno, & Thiele, 2015, p. 1247). For this reason, it is important to understand the effects that CBD will have when taken concomitantly with Clobazam. Both CBD and Clobazam are metabolized by the family of P450-complex enzymes in the liver. Clinical trials that have investigated the pharmacokinetics of Clobazam when administered together with other P450-complex inhibitors showed the potential for clinically significant drug-drug interactions. Researchers at Massachusetts General Hospital conducted a study that included thirteen patients with refractory epilepsy taking a combination of Clobazam and CBD. Research findings indicate that through the inhibition of liver enzymes and the subsequent partial metabolism of Clobazam, CBD acted to elevate plasma concentrations of the antiepileptic drug. Over the study period, nine of the thirteen subjects experienced a greater than 50% decrease in seizures. This decrease in seizure frequency occurred even though Clobazam doses were reduced for ten of the thirteen study participants. Side effects were documented in 77% of the subjects, but were completely resolved when Clobazam dosages were reduced (Geffrey et al., 2015). In June 2018, the FDA approved Epidiolex, a CBD oral solution for the treatment of two rare and severe forms of epilepsy called Lennox-Gastaut and Dravet syndromes.

## Conclusion

During the last five decades, research related to CBD has demonstrated that this plant-based cannabinoid offers a "wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials" (Zuardi, 2008, p. 277). The wealth of health benefits presented in the scientific literature relating to CBD make this an attractive option for those seeking alternative care options. The immense potential that CBD is showing throughout the research reviewed is primarily related to its direct interaction with the now better understood and appreciated body system called the endocannabinoid system. CBD shows particular promise due to the wide-ranging potential that it is showing coupled with its excellent safety profile, as stated by researchers.

## References

Bergamaschi, M. M., Queiroz, R. H., Zuardi, A. W., & Crippa, J. A. (2011). Safety and side effects of cannabidiol, a cannabis sativa constituent [Abstract]. *Current Drug Safety, 6*(4), 237-249.

Geffrey, A. L., Pollack, S. F., Bruno, P. L., & Thiele, E. A. (2015). Drug-drug interactions between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia, 56*(8), 1246-1251. doi:10.1111/epi.13060

Grayson, L., Vines, B., Nichol, K., & Szaflarski, J. P. (2018). An interaction between warfarin and cannabidiol, a case report. *Epilepsy & Behavior Case Reports, 9,* 10-11.

Iffland, K., & Grotenhermen, F. (2017). An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. *Cannabis and Cannabinoid Research, 2*(1), 139-154. doi:10.1089/can.2016.0034

Katsidoni, V., Anagnostou, I., & Panagis, G. (2013). Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus [Abstract]. *Addiction Biology, 18*(2), 286-292.

Lucas, C. J., Galettis, P., & Schneider, J. (2018). The Pharmacokinetics and the Pharmacodynamics of Cannabinoids. *British Journal of Clinical Pharmacology*. doi:10.1111/bcp.13710

Manini, A. F., Yiannoulos, G., Bergamaschi, M. M., Hernandez, S., Olmedo, R., & Barnes, A. J., et al. (2015). Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *Journal of Addiction Medicine, 9*(3), 204-210.

Maroon, J., & Bost, J. (2018). Review of the neurological benefits of phytocannabinoids. *Surgical Neurology International, 9*, 91. http://doi.org/10.4103/sni.sni_45_18

Mehvar, R. (2018). Clearance concepts: fundamentals and application to pharmacokinetic behavior of drugs. *Journal of Pharmacy & Pharmaceutical Sciences, 21*(1s), 88s-102s. doi:10.18433/jpps29896

National Institute on Drug Abuse. (2018). *Opioid overdose crisis*. Retrieved July 30, 2018, from http://www.drugabuse.gov/drugs-abuse/opioid-overdose-crisis

Noreen, N., Muhammad, F., Akhtar, B., Azam, F., & Anwar, M. I. (2018). Is cannabidiol a promising substance for new drug development? A review of its potential therapeutic applications [Abstract]. *Critical Reviews in Eukaryotic Gene Expression, 28*(1), 73-86. doi:10.1615/CritRevEukaryotGeneExpr.2018021528

Stott. C., White, L., Wright, S., Wilbraham, D., & Guy, G. (2013). A phase-I, open-label, randomized, crossover study in three parallel groups to evaluate the effects of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus, 2*, 1-15. doi:10.1186/2193-1801-2-236

Wada.-ama.org. The world anti-doping code international standard prohibited list. 2018. Retrieved August 14, 2018, from https://www.wadaama.org/sites/default/files/prohibited_list_2018_en.pdf

Zuardi, A. W. (2008). Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Revista Brasileira de Psiquiatria, 30*(3), 271-280.