



A PROJECT CBD PUBLICATION

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Published: September 25, 2018

Last updated: September 25, 2018

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# EDITOR'S NOTE

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Cannabis is one of the most widely consumed substances in the United States and throughout the world. But it is difficult to access pertinent information about cannabinoid-drug interactions because of marijuana prohibition and consequent restrictions on clinically relevant research.

Drug interactions are a complicated issue. More than half of U.S. adults regularly take prescription meds and at least 75 percent of Americans take at least one over-the-counter drug. Most seniors and many others take multiple drugs, and many of these can affect the metabolism of each other. Seniors are also the fastest growing demographic of cannabis users.

Given the widespread use of medical cannabis, it's important for physicians and patients to understand how THC, CBD, and other cannabis components interact with many commonly used pharmaceuticals—not only to anticipate and avoid problematic outcomes, but also to take advantage of situations where cannabis and pharmaceuticals can interact in a positive way.

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# PART 1: AN INTRODUCTION TO DRUG INTERACTIONS

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Drug interactions are an important consideration in medicine. Although they are rarely so dangerous as to entirely preclude the use of a medication, they can have serious impacts on a patient's treatment and wellbeing.

There are three main ways by which two drugs can interact:

- 1) **Metabolic interactions.** One drug can affect the metabolism of another drug, thereby prolonging or reducing the activity, intensity, and side effects of the latter.
- 2) **Drug distribution.** A drug can change how a second drug is absorbed and distributed throughout the body.
- 3) **Convergent pathways.** Two drugs may work through convergent or similar biological pathways, which could lead to antagonistic or synergistic effects. In order to predict convergent drug interactions both drugs need to be well studied.

Some drug interactions can be understood by looking at the properties of a single compound. For example, if we know how cannabidiol (CBD), a non-intoxicating component of cannabis, inhibits drug-metabolizing enzymes, then we can foresee certain interactions. Or, knowing how tetrahydrocannabinol (THC), the main

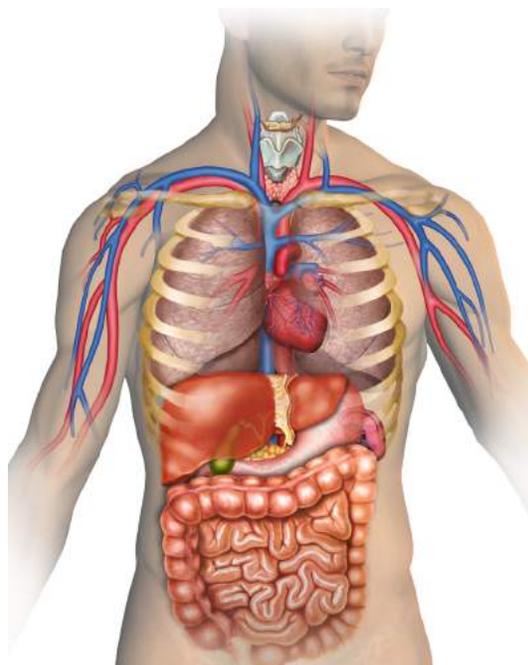
psychoactive component of cannabis, modulates absorption through the gut would allow us to predict whether or not THC will affect another drug.

Such information can help doctors recognize if extra caution is necessary when recommending the use or cessation of cannabinoid therapies.

## Cytochrome P450

One of the largest classes of drug-metabolizing enzymes is the cytochrome P450 (abbreviated CYP, pronounced 'sip') family. CYP isoforms are non-specific enzymes, meaning they can bind and metabolize many different chemical substrates. Cytochrome P450 enzymes usually make chemicals more water-soluble and are involved in metabolizing an estimated 60 to 80 percent of all pharmaceuticals.

While CYPs are most heavily expressed in the liver, the principal organ involved in drug metabolism, some other tissues contain significant concentrations of these metabolic enzymes<sup>1</sup>. CYP1 enzymes, for example, are present in the lungs. Orally consumed drugs are absorbed through the intestinal tract, where CYPs are also expressed.



***CYPs are most heavily expressed in the liver but are also present in the lungs, and intestinal tract.***

If a cannabinoid such as CBD or THC *inhibits* a CYP enzyme, then the metabolism of the other drug will be delayed and its level may increase.

If a cannabinoid *induces* a CYP enzyme, causing more of the enzyme to be made, this will shorten the lifespan of another drug that is a substrate for the same CYP.

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<sup>1</sup> CYP enzymes don't simply exist in the liver; they reside in certain subcellular compartments in liver cells called the endoplasmic reticulum. A recent presentation at the 2018 International Cannabinoid Research Society suggested that the fatty-acid binding protein 1 (FABP1) has to shuttle cannabinoids to CYP enzymes inside the cell. FABPs are also required to transport endocannabinoids into the cell so they can act on nuclear receptors or be degraded.

## Modulatory Effects

There are various ways of modulating CYP enzymes. In preclinical studies, CBD is able to influence CYPs through most of the methods below:

- ◆ **Competitive inhibition.** A chemical can bind to a CYP but not react with it, thereby blocking the other drug from entering the active site of the enzyme, where the metabolic reaction would ordinarily occur.
- ◆ **Allosteric modulation.** A chemical can change how well a second molecule fits into the enzyme, either enhancing or decreasing the enzyme's binding affinity with a pharmaceutical ligand.
- ◆ **Heteroactivation.** Certain CYP enzymes, such as CYP3A4, may not metabolize a drug normally, but a second chemical may change the shape of CYP3A4 so that it can metabolize a drug that it otherwise would not. This is an extreme case of allosteric modulation.
- ◆ **Enzyme disintegration.** Some drugs cause the essential components of a CYP enzyme to dissociate, thereby rendering the enzyme nonfunctional.
- ◆ **Altered gene expression.** A compound may affect the gene encoding a CYP enzyme, increasing or decreasing the total amount of the enzyme in the cell.

These modulatory effects often depend on the second drug that the cannabinoid interacts with. This can get very complicated.

What may cause competitive inhibition in one cannabinoid-drug interaction could actually promote metabolism in another type of interaction. For example, CBD increases the metabolism of the antiepileptic drug (S)-mephenytoin via CYP3A4, but appears to inhibit the metabolism of cyclosporin through the very same enzyme.

Another complication: Some pharmaceuticals, called prodrugs, don't become functional until they are metabolized into an active component. If CBD or THC slows the breakdown of a prodrug, it will remain inactive—whereas inhibiting metabolism of a regular drug will result in higher blood levels of the active substance.

When used for an extended period, many CYP inhibitors will cause genetic induction. This can sometimes balance the effect of drug interactions. Hence, doctors



*Prodrugs don't become functional until they are metabolized into an active component.*

may find that the effect of cannabinoids on other drugs will change or stabilize over the course of one to two weeks.

All these variables make precise predictions of drug interactions difficult, even for practiced physicians. It is much easier to assess whether drug interactions are likely than to predict their exact effect.

## Case Report: Warfarin

Despite many complex details, drug interactions can be relatively simple to manage, as indicated in a recent case report<sup>2</sup> involving CBD and warfarin, a widely-prescribed blood-thinner sold as Coumadin.

It is estimated that there are over 60,000 emergency room visits in the US each year due to warfarin, which is notoriously challenging to dose. A report published in February 2018 describes a patient who was taking 7.5 mg warfarin per day. The patient began using a pure CBD tincture called Epidiolex, the dose of which was increased to 15 mg/kg over a month. CBD inhibited the metabolism of the blood thinner, which caused the patient's warfarin concentrations to increase.<sup>3</sup> Therefore, the dose of warfarin was decreased by 20 percent.

But over the next nine months, the amount of CBD was increased to 35 mg/kg (1800 mg CBD), so the warfarin dose had to be changed a number of times, finally settling at 71 percent of the original dose. Although warfarin is a drug with a significant risk of complications—particularly bleeding—none were seen in this case study, which was performed by researchers at the University of Alabama in Birmingham. This illustrates how physicians can manage cannabinoid-drug interactions.

Another example came to light during a clinical trial with Epidiolex, which has been approved by the FDA for treating certain kinds of epilepsy. One downside of this single-molecule formulation is that high doses are required, up to 50 mg/kg/day.<sup>4</sup> Clobazam is one of many anti-epileptic drugs. Although it is active, its metabolite, N-desmethyloclobazam (nCLB), also confers anti-seizure activity. Therapeutic doses of Epidiolex increased the levels of nCLB, so the dose of clobazam had to be reduced for some children.

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<sup>2</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5789126/pdf/main.pdf>

<sup>3</sup> Warfarin concentrations are described by the International Normalization Ratio, INR, which should be between 2-3. This is the number doctors use to adjust the dose.

<sup>4</sup> For an adult weighing 60 kg (132 lbs), this dose is equivalent to of 3000 mg CBD. (By comparison, a typical starting dose of THC is 1 to 5 mg.) The target range of Epidiolex in this trial was initially 5 to 25 mg CBD/kg/day, but the maximal dose was increased to 50 mg/kg/day in subsequent studies.

Many medications are safe, but those with dangerous side effects or a narrow therapeutic window (where there's not much difference between the effective dose of a drug and the toxic dose) should be monitored to adjust for potential drug interactions when they arise. Once the dose of each drug has stabilized, the monitoring can usually be stopped.

## How to Use This Information

One does not need to learn the subtleties of drug interactions in order to get a sense of whether cannabis or a particular plant cannabinoid will interact with a given medication. The information given in this primer may help alert doctors and patients to interactions that are likely.

For an initial approximation of whether a cannabinoid will interact with a drug, one should check if they are both metabolized by the same CYP enzymes.

In the United States, the main ways that any drug is metabolized are studied before that drug's approval. Pharmaceutical companies must assess potential drug-drug interactions for all new medications. Generally, this will include information on which CYP enzymes, if any, break down the pharmaceutical. When this is known, a patient or doctor can look into how cannabinoids modulate that group of CYPs.



*It is important to consider the dosage of cannabinoids used when discussing the potency of CYP inhibition.*

Hopefully, this knowledge can help prepare physicians to spot changes in drug clearance and adjust a patient's dose accordingly.

## Reading Research: Important Caveats

Phytocannabinoids interact with CYPs in a variety of ways. The vast majority of studies on how cannabinoids interact with CYPs are preclinical—their results are a starting place, not definitive proof that interactions will occur. And while preclinical data provides an indication of which drugs may interact with CBD and other cannabinoids, it is difficult to predict the effect of these interactions. As well, the doses used in preclinical studies rarely translate to human experience.

Of all the data in preclinical studies of CYP inhibition, the ' $K_i$ ' (pronounced 'K-I') is one of the most important values. The  $K_i$  for CBD's inhibition of a CYP indicates CBD's potency.<sup>5</sup> The smaller the  $K_i$ , the more potent the inhibition.

Although the  $K_i$  suggests the degree to which CBD will modulate a CYP, it cannot be used to determine an exact dose at which cannabidiol could become problematic because it is inhibiting a CYP. This depends on how CBD is administered, the second drug in question, the condition of the individual's liver, and many other factors.

The  $K_i$  for the inhibition of various CYPs by three phytocannabinoids—CBD, THC, and CBN—is shown in Appendix B. An assessment of cannabinoid activity relative to these CYPs, roughly in order of potency, is included in the sections that follow. The  $K_i$ s can be used to suggest the relative importance of different CYPs, but shouldn't be compared to effects of cannabinoids that aren't mediated by the liver, like THC's potency at CB1 (which causes the high).<sup>6</sup>

As well, it is important to consider the dosage of cannabinoids used when discussing the potency of CYP inhibition. Oral THC is given at doses of 1 to 10 mg in naïve patients, whereas doses of CBD typically range from 5 to 500 mg—with CBD doses as high as 2000 mg not uncommon. *So even in situations where THC is more potent than CBD, the fact that some people tend to use much higher doses of CBD makes it a riskier player in metabolic drug interactions.*

The way cannabinoids are administered (e.g. smoking, eating, etc.) also has a major impact on whether or not drug interactions occur.

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5 Intuitively, the  $K_i$  is the concentration of CBD required to inhibit 50 percent of the enzyme's activity, normalized to the concentration of the other drug. It varies with different primary substrates.

6 It is hard to relate the potencies of different effects of a compound—one cannot simply compare THC's inhibition of CYPs to its psychoactivity because the former interaction occurs in the liver, whereas the latter occurs in the brain. So, relative potencies must be adjusted by considering how the cannabinoid separates into different parts of the body. This should depend on how the cannabinoids are taken (e.g. smoked, vaporized, eaten, etc.), but it has not been well studied for any mode of administration. Differences in the affinity for transport molecules that bring cannabinoids to CYPs may also affect the measured potency.



# PART 2: CYP SPECIFICS

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## The CYP1 Family (CYP1A1, 1A2, 1B1)

CYPs 1A1, 1A2, and 1B1 are present primarily in the liver and lungs. In the lungs these CYPs convert many chemicals from tobacco, cannabis and other kinds of smoke into more potent carcinogens, including polycyclic aromatic hydrocarbons (PAHs). PAHs are present in both tobacco and cannabis smoke. PAHs also induce (promote) CYP1 activity, which amplifies their carcinogenic potential.

THC inhibits the CYP1 family at moderate concentrations that are likely to occur when cannabis is vaporized or dabbed. When cannabis is smoked, the inhibitory effect of THC may counter the inductive effects of PAHs. In other words, the smoke and the THC may mitigate each other's effects on CYP1 enzymes. This may contribute to the anticancer properties of cannabis with respect to lung cancer, specifically.

Cannabinol (CBN), which forms as THC ages, is a very potent inhibitor of CYPs 1A1, 1A2, and 1B1. CBD also inhibits 1A1 with high potency, but not as



***PAHs (polycyclic aromatic hydrocarbons) promote CYP1 activity, which amplifies the carcinogenic potential of toxins in smoke.***

powerfully as CBN. Although CBD is less potent than CBN, it appears to act much quicker.

In one study, CBD was a stronger inhibitor of the CYP1 family when given 20 minutes *before* the second drug, whereas the timing of applying THC and CBN did not affect their inhibitory potency.<sup>7</sup> In addition, high concentrations of CBD or THC increased the transcription of the gene for CYP1A, thereby boosting the production of these enzymes a day later.

In the liver, CYP1 enzymes also metabolize caffeine, melatonin, and a number of pharmaceuticals. Whether CBD is inhaled or ingested, drug interactions with CYP1 are less likely if CBD is administered *after* the other drug. A cannabis-infused edible may also slow drug metabolism, which in the case of THC could intensify and prolong the effect of caffeine, for example.<sup>8</sup>

## The CYP2C Family (CYP2C9, 2C19)

With regard to cannabinoids, the two significant CYPs in the 2C family are 2C9 and 2C19. These enzymes metabolize many antiepileptic drugs, phytocannabinoids (including THC and CBD), and some endocannabinoids, as well as non-steroidal anti-inflammatory drugs, warfarin, diazepam, and other pharmaceuticals.

Both 2C9 and 2C19 are highly polymorphic. Common genetic variants of 2C9 have only 30 percent of the activity of the normal enzyme, and there exist both overactive and underactive variants of 2C19.<sup>9</sup>

Individuals with less functional CYP2C enzymes are likely to experience more significant cannabinoid-drug interactions and will experience interactions at lower doses, as the baseline activity of these enzymes is already closer to their maximal activity.

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- 7 In the referenced study, applying cannabidiol 20 minutes before the second drug made CBD 2-3 times more potent. One explanation is that a metabolite of CBD may be a stronger CYP1 inhibitor than CBD itself.
  - 8 CBD is less likely to intensify the effects of caffeine because it may counteract some of caffeine's effect on adenosine receptors. Caffeine is a stimulant because it blocks adenosine receptors. But at high doses CBD delays the cellular reuptake of adenosine, prolonging its action at adenosine receptors. This may be partly responsible for CBD's sedative effects at high doses.
  - 9 This may help explain why some individuals are very sensitive to THC. THC is metabolized to 11-OH-THC primarily by CYP2C9, though CYP3A4 does this as well. But 11-OH-THC is more psychoactive than THC, either because it binds to CB1 with more strength than THC or because it accumulates more in the brain. Then CYP3A4 breaks down 11-OH-THC further to a non-psychoactive chemical (11-COOH-THC). If CYP2C9 is underactive due to a genetic mutation, then CYP3A4 will shoulder the burden of turning THC into the more psychoactive 11-OH-THC, and may be slower to create the non-psychoactive metabolite.

THC, CBD, and CBN all inhibit CYPs 2C9 and 2C19 with moderate or low potency. While CBD and CBN appear to inhibit 2C enzymes competitively, THC inhibits them in a mixed manner (partially competitive, partially via an allosteric interaction). This suggests that THC will have a more varied effect on drugs metabolized by 2C9 and 2C19.

THC at low concentrations (around 0.01 – 0.1  $\mu\text{M}$ ) is an inducer of 2C9. This dose is similar to the potency with which THC activates CB1 receptors and causes a high. The metabolites of THC can induce 2C9, as well. In other words, if there is enough THC to cause a high, then CYP2C9 is probably being affected.

Even with relatively low doses of THC, these enzymes are likely to become more active, thereby increasing the clearance of CYP2C-metabolized drugs. But THC's inhibitory effect with respect to CYP2C could become dominant with moderate to high doses of THC—or when CBD or CBN are used in conjunction with THC.



***While CBD isolates like Epidiolex have caused significant interactions with anti-epileptic drugs, whole-plant extracts generally have not.***

There is likely an intermediate range where the positive and negative effects balance each other, leading to no overall effect. *This may explain why isolate CBD (e.g. Epidiolex) has caused significant interactions with anti-epileptic drugs, whereas whole-plant extracts generally have not.*

CBD was a stronger inhibitor of CYP2C19 than CYP2C9. This makes sense, as 2C19 is involved in the body's metabolism of CBD, whereas 2C9 is involved in breaking down THC. According to some research, CBD also induces the 2C family, but surprisingly this did not lead to an overall increase in 2C activity in one such study. Why not? Perhaps because CBD's amplification of CYP2C is counteracted by CBD's competitive inhibition of these same enzymes. More research on how chronic use of CBD affects the CYP2C family is needed to better understand these dynamics and their relevance for drug interactions.

One way or another, there is a clear potential for drug interactions with individual cannabinoids due to CYP2C9 and CYP2C19. The genetic variability of patients' 2C9 and 2C19 enzymes as well as the specific dose and ratio of cannabinoids will play a significant role in phytocannabinoid-drug interactions.

## The CYP3A Family (CYP3A4, 3A5)

The CYP3A family is perhaps the most significant group of CYP enzymes. CYP3A4 catalyzes the metabolism of approximately 30 percent of all pharmaceuticals. It is primarily distributed in the intestines and liver, so orally administered drugs are actually metabolized by 3A4 twice before circulating throughout the body. (This is called “first-pass metabolism.”) Grapefruit’s potent drug interactions are due to its dual inhibition of intestinal and liver 3A4.

Interactions with 3A4 are generally substrate specific, meaning that a compound like CBD can either increase or decrease 3A4 activity, depending on the second drug. CYP3A4 is one of the main enzymes involved in the metabolism of CBD and THC (along with CYPs 2C19 and 2C9, respectively).

CBD modulates CYP3A4 and 3A5. From preclinical research, it appears that low to moderate doses of CBD can inhibit both of these enzymes. This is based on cellular studies of how CBD inhibits the metabolism of diltiazem (a drug prescribed for hypertension). But it is very likely that the effect and potency of CBD will change depending on the second drug in question.

THC and CBN at normal doses are unlikely to interact with 3A-metabolized drugs. Although THC and CBN are weak inhibitors of 3A4/5, CBD appears to activate 3A4 with respect to certain drugs (mephenytoin and indinavir) and to inhibit 3A4 with respect to others (e.g. cyclosporin, diltiazem). CBD can also genetically induce 3A, which balanced the inhibitory effects of CBD in one study from the 1980s.<sup>10</sup>

One of the only clinically studied cases of CBD-drug interactions was seen with clobazam, an anti-epileptic prodrug, which is metabolized by CYP3A4 to the active compound N-desmethyloclobazam. It appears that CBD increases the production of the active compound by potentiating 3A4 activity while simultaneously inhibiting CYP2C19, which breaks down N-desmethyloclobazam.

While interactions between CBD and 3A4-metabolized drugs are possible, several variables make it difficult to predict the exact effect. But interactions are far more likely when both drugs are taken orally.

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<sup>10</sup> No mechanism for CBD’s induction of CYP3A was suggested in this study. Sometimes the body tries to compensate for inhibitors by overexpressing the inhibited enzyme. Other work has indicated that a nuclear receptor called PPAR $\alpha$  (pronounced ‘P-par-alpha’) increases the synthesis of some CYPs, including 3A4, 2B10, and 1A1. CBD indirectly activates PPAR $\alpha$  by augmenting the level of other endocannabinoid-like chemicals.

## The CYP2B Family (CYP2B1, 2B6, 2B10, 2B13)

The 2B family metabolizes a variety of chemicals, including many pesticides, valproate, methadone, ketamine, and anesthetics. CBD can significantly modulate 2B enzymes, particularly 2B6, 2B10, and 2B13.

CBD inhibits CYP2B6 with low to moderate potency. And at very high doses, CBD is also an inducer of 2B10 and 2B13, increasing the production of these enzymes between 10-60 fold in different studies. One of CBD's CYP-generated metabolites, 6 $\alpha$ -OH-CBD, also induces CYP2B10 (potentially via PPAR $\alpha$ ; see footnote 10). The induction of these enzymes occurs with acute CBD administration, in contrast to the usual pattern of CYP induction, which typically occurs in response to long-term use of a drug.

CYP2B-metabolized drugs, especially those metabolized by 2B10 and 2B13, are likely to have significantly increased clearance when co-administered with high doses of CBD. Drug interactions are also possible with 2B6-metabolized enzymes, such as some opiates or the pesticides permitted for use on cannabis in certain US states.

In clinical trials of Epidiolex for pediatric epilepsy, some children used both CBD and valproate. The changes in valproate metabolism appeared insignificant, although the data suggested that CBD might exacerbate liver dysfunction caused by valproate. This is not cause for immediate alarm in patients using CBD-rich cannabis or CBD extracts. But it certainly warrants caution and follow-up studies.

Studies of THC and CBN suggest that they have some effect on CYP2B, but are roughly one fifth as potent as CBD. THC is often given at much lower doses than CBD. And CBN, a breakdown product of THC, is rarely used intentionally. Thus, neither THC nor CBN figure prominently in 2B-dependent drug interactions.

Limited preclinical research also suggests that aromatic terpenes in the cannabis plant—including  $\alpha$ -pinene,  $\beta$ -caryophyllene,  $\beta$ -myrcene, and limonene—can both induce and inhibit CYP2B1, whereas CBD does not appear to modulate CYP2B1<sup>11</sup>. It is unclear to what extent this is clinically significant, since terpenes are present in much smaller concentrations than cannabinoids and the terpene profile of cannabis varies widely from plant to plant.

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11 Anandamide, one of the major endocannabinoids, may induce CYP2B1/2 as well. This is not likely to be relevant for drug interactions, as anandamide is synthesized and destroyed “on demand” and does not circulate throughout the body.

## **CYP2D6**

CYP2D6 metabolizes many opiates, antipsychotics, and antidepressants (both tricyclic antidepressants and SSRIs). Given that CBD has shown promise as an anxiolytic, antipsychotic, and anti-nociceptive agent, chances are that it will be administered with 2D-metabolized drugs.

CYP2D6 also activates the prodrug tamoxifen, a pharmaceutical treatment for breast cancer. Since CBD inhibits the ID-1 gene, which can reduce the metastasis of breast cancers, it is worth studying potential interactions.

Cannabidiol is able to inhibit CYP2D6 at moderate to high doses similar to the 2C family. Not much else about cannabinoid-2D6 interactions has been established.

It is also likely that CBD will interact with some pharmaceuticals by modulating the neurotransmitter systems upon which these drugs act. For example, CBD increases the activity of serotonin receptors, which are targets of many anti-depressants.

## **CYP2J2**

CYP2J2 has minimal activity in the liver, but is expressed in regions of the heart, brain, and pancreas. It breaks down some antihistamines (allergy medication), but also has a role in endocannabinoid regulation.

THC, CBD, and CBN are all inhibitors of CYP2J2 with moderate or high potency.

CYP2J2 is able to metabolize arachidonic acid, the major breakdown product of endocannabinoids, as well as some endocannabinoids themselves. The 2J2-catalyzed metabolites of arachidonic acid may regulate cannabinoid receptors in the heart and brain. But CYP2J2 is a relatively minor player in pharmaceutical metabolism, so it is unlikely to be relevant for most cannabinoid-drug interactions.



# PART 3: ADDITIONAL CONSIDERATIONS

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## **Less Effective or More Dangerous?**

When cannabinoids are added to someone's existing medications, what actually happens? At first, cannabinoids interact with some CYPs, as described above. This will usually begin within 10 minutes to 2 hours, depending on whether the cannabinoids are smoked or swallowed or absorbed sublingually.

The immediate interaction usually decreases drug metabolism via CYP inhibition, but in some cases (with 2B10/13, 2C9, 3A4) it may increase metabolism. Moreover, metabolism may be an integral step in activating the drug if the medications are prodrugs. Some drugs (such as those metabolized by CYP1A) are more sensitive to cannabinoids when the cannabinoids are taken first.

Over the course of a day to a few weeks, some of the inhibited CYPs may become overexpressed in an attempt to restore homeostasis and normal baseline activity. Certain CYPs (1A, 2C9, 2C19, 3A4/5) will likely regain some of their activity, but this might not be enough to compensate for the inhibition due to long-term cannabinoid administration. At the same time, three other factors start to come into play.

- ◆ The body may develop tolerance to the inhibition of CYPs. This can happen when very high doses of cannabinoids are consumed on a regular basis, though the effect of low-dose cannabinoids is unknown.

- ◆ Cannabinoids will likely reduce inflammation, which can increase the activity of some CYP enzymes.<sup>12</sup>
- ◆ CBD, which regulates the expression of at least 1200 genes, may modify the expression of certain CYPs.

These factors could balance some of the inhibitory effects of cannabinoids with respect to CYPs, but may also lead to over-compensation of CYP activity. In order to understand enough details to make specific predictions, clinical studies examining specific cannabinoid-drug interactions are necessary.

## Modes of Administration

The way cannabis is consumed adds another layer to the complexity of drug interactions. Cannabinoids can be smoked, vaporized, eaten, rubbed on skin, absorbed under the tongue, etc. From a reductionist perspective, the mode of administration affects the maximal amount of cannabinoids in the liver and how quickly they get there. Some models of cannabinoid use have attempted to describe these quantities—called the  $C_{\max}$  and  $t_{\max}$  respectively—in the blood, but no model exists which accurately predict liver concentration. (It is a lot easier to draw blood than take a liver biopsy, after all.)

### **Smoking and Vaping**

Inhaled cannabinoids will go through the lungs (where the CYP1 family is present) into the bloodstream, directly towards the brain and heart. Then they will slowly pass through the liver. Changes in drug metabolism—if they are to occur at all—would likely begin within minutes of inhalation. Inhibition of CYP1 is very likely. A few hours after smoking, the risk of drug interactions will be much lower. Vaporized cannabis may have a somewhat different effect than smoked cannabis. Compared to smoking, vaporizing cannabis bud usually results in a slightly higher dose and slower absorption. Right now, no research has compared vaporizing cannabis oil extracts with vaporizing or smoking flower.

### **Ingestion**

Ingested cannabinoids are primarily absorbed through the intestines (where CYP3A is present) and then are processed by the liver before being distributed through the body. Cannabinoids are absorbed more if ingested on a full stomach, but the absorption is slower in this case. The  $t_{\max}$  (the time it takes to be processed by the liver and absorbed into the bloodstream) usually ranges from 2 to 4 hours. Ingestion has three important distinctions from inhalation:

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12 One effect of chronic stress and inflammation is a change in liver function. CYP activity is generally reduced by ongoing inflammation. Cannabinoids reduce this stress, which may restore some CYP activity.

- ◆ Ingested cannabinoids will have higher peak liver concentrations than inhaled cannabinoids, so ingested cannabinoids should have more potent drug interactions.
- ◆ Ingested cannabinoids will have a greater effect on CYP3A-metabolized drugs, as they interact with CYP3A in both the intestines and liver.
- ◆ After being processed by the liver, ingested cannabinoids will largely be converted to their metabolites. So, the effects of ingested cannabinoids will depend on less studied cannabinoids like 11-OH-THC and 7-COOH-CBD, major metabolites of THC and CBD, respectively. Some of these metabolites also interact with CYPs.

### ***Oral-Mucosal and Sublingual***

Oral-mucosal administration is a middle ground between inhalation and ingestion. If taken correctly, oral-mucosal drugs are absorbed through membranes in the mouth (under the tongue and along the cheek) without swallowing. These come in the form of tinctures and under-the-tongue sprays, among other delivery systems.

When administered sublingually, cannabinoids aren't immediately processed by the liver—like ingested drugs—but neither do they go directly to the brain and heart—like inhaled drugs. They are just absorbed into the bloodstream. Many sublingual drugs have a  $t_{max}$  around 15 minutes. With cannabis tinctures, however, studies suggest that the  $t_{max}$  is around 2 hours, more like oral administration. It is unclear if this is because patients accidentally swallow the tincture or if the diffusion of cannabinoids is just slower than most other drugs.

### ***Topical***

Although topical cannabinoids can be absorbed through the skin into joints, they do not get into the bloodstream. As such, there is no potential for metabolic drug interactions.

### ***Transdermal***

Transdermal administration of cannabinoids is quite different than a regular topical application. A transdermal patch will slowly release cannabinoids into the bloodstream, usually at a constant rate. As with sublingual and inhaled cannabinoids, the liver concentration of cannabinoids should roughly parallel their concentration in the blood. The  $t_{max}$  and  $C_{max}$  will depend on the precise formulation.

## **Other Clinical Examples**

A small number of clinical trials have specifically evaluated the risks of cannabinoid-drug interactions with opiates, anti-epileptic drugs, and antiretroviral therapies. Although cannabinoids only had a slight impact on drug metabolism in most of these studies, the results were clinically significant with respect to some anti-epileptic drugs.

- ◆ When individuals taking 50-60 mg morphine or oxycodone also vaporized THC-rich cannabis, there was no change in total opiate exposure, a slight decrease in maximal morphine concentration, and significantly lower ratings of pain.
- ◆ Patients with HIV taking indinavir or nelfinavir either smoked THC-rich cannabis or ingested 2.5 mg of pure THC. Ingested THC had no effect on the concentration of the anti-HIV drugs, but smoked cannabis decreased the maximum concentration of indinavir. According to the authors, “the magnitude of changes...are likely to have no short-term clinical consequences. The use of marijuana or dronabinol [isolate THC] is unlikely to impact antiretroviral efficacy.”
- ◆ Individuals ingested 400 mg or 800 mg of pure CBD one hour before being injected with up to 1 µg/kg fentanyl. CBD was not associated with any measures of opiate toxicity. This study, however, did not directly assay blood concentration of fentanyl.

A number of interactions have been noted between a formulation of pure cannabidiol, Epidiolex, and anti-epileptic drugs, as described earlier. This may be—in part—because very high doses have been used in many of the Epidiolex trials. It is also likely due to simultaneous interactions with three sets of CYP enzymes: CYP3A4 in the intestines, CYP3A4 in the liver, and CYP2C19 in the liver.

In 2015, researchers at Massachusetts General Hospital described a significant interaction with clobazam, a benzodiazepine. CYP3A4 metabolizes clobazam to an active metabolite, N-desmethyloclobazam (nCLB), and CYP2C19 further breaks down nCLB. Cannabidiol increased nCLB concentrations by 500%, possibly by activating CYP3A4 activity while simultaneously inhibiting CYP2C19. But these authors conclude that “CBD is a safe and effective treatment of refractory epilepsy in patients on clobazam treatment,” although “monitoring of clobazam and nCLB levels is necessary.”

Since this report, another study on the interaction between Epidiolex and anti-epileptic drugs has been published. CBD caused statistically significant changes in the concentration of a number of anti-epileptic drugs: clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine. Clobazam was the only drug whose concentration moved outside of the therapeutic window (roughly the range of concentrations where the effectiveness of the drug outweighs its side effects or toxicity). In particular, nCLB levels rose by about 100%, so the dose of clobazam had to be decreased.

Patients taking CBD with valproate had abnormal liver function, as discussed in the section on the CYP2B family. Adults had slightly different drug-interactions than children.

## Cannabinoid-Cannabinoid Interactions

There are a multitude of ways in which different cannabinoids (like THC and CBD) can interact. These interactions contribute to the “entourage effect,” in which the effects of various cannabinoids, terpenes, and other plant compounds combine synergistically, often ameliorating some side effects while enhancing therapeutic actions.

Both clinical and preclinical work has suggested that compared with isolate cannabinoids, cannabis extracts generally require smaller doses to be effective, have a broader range of therapeutic doses, have a more powerful effect, and have less severe side effects.<sup>13</sup>

What gives rise to the entourage effect? To fully understand, one would need to compare the chemical mechanisms by which cannabinoids move and act throughout the body, and then study how cannabinoids could regulate each other. But the metabolic interactions between CBD and THC are a more comprehensible example: THC is metabolized primarily by two CYP enzymes: CYP2C9 turns THC into a slightly more psychoactive chemical called 11-OH-THC, and then CYP3A4 breaks this down to 11-COOH-THC, a nonpsychoactive chemical that is thought to have anti-inflammatory effects.

CBD is also metabolized mainly by two CYPs: CYP2C19 converts CBD to 7-OH-CBD, and CYP3A4 then turns this into 7-COOH-CBD.<sup>14</sup> The metabolites of CBD are not well-characterized. By taking CBD and THC together, individuals may find that the effects of THC are tempered but prolonged slightly. CBD's inhibition of CYP3A4 would be responsible for the extension of THC's effects, while the inhibition of CYP2C9 may blunt the high caused by THC.<sup>15</sup>



*The “entourage effect” refers to the way in which various plant compounds combine synergistically.*

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13 Although there is a body of work suggesting this, some specific effects are very mixed. For example, CBD has been shown to increase the appetite stimulation caused by THC in one study, and increase the appetite suppression from THC in another. Whether combinations are good or bad also depends on what effects the individual is seeking.

14 The ‘7’ position of CBD is in the same place as the ‘11’ position of THC. The different numbers are due to a naming convention in chemistry.

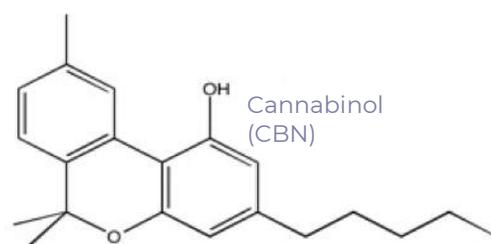
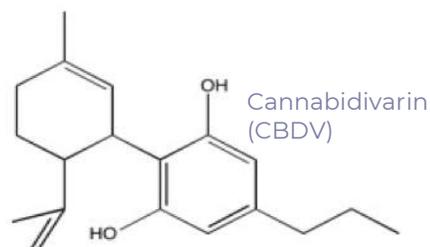
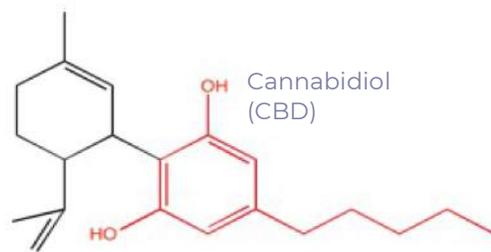
15 Other effects of CBD come into play here as well. For example, CBD can increase adenosine levels in the hippocampus which would likely prevent memory issues due to THC. There is also preclinical evidence

## The Chemistry of CYP Inhibition

Extensive preclinical work by Satoshi Yamaori, Kazuhito Watanabe, and other researchers at Hokuriku University has shed light on the chemical features of CBD that allow it to inhibit various CYPs. This is very useful information for groups trying to design new drugs based on phytocannabinoids, and can also help to predict whether other, yet untested plant cannabinoids will inhibit CYPs and cause drug interactions. The structure of CBD is shown in figure 1.

The pentylresorcinol moiety, highlighted in red, is one of the key features causing CBD to inhibit many CYPs. Other cannabinoids with alterations in this structure have predictably different potencies inhibiting CYPs. Specifically, if either hydroxyl (the OH attached to carbon) is modified, CBD's potency as an inhibitor of several CYP families decreases to roughly 20 percent. THC, lacking a free hydroxyl, is a less potent inhibitor of these CYPs compared to CBD. Both hydroxyls of CBD are required for the potent inhibition of CYPs 1A1, 2B6, 2D6, 3A4, and 3A5, but not for 2C9, 2C19, and 2J2.

**Figure of five common plant cannabinoids. The “pentylresorcinol” or “olivetol” moiety is highlighted in red. Both the free hydroxyls as well as the 5-carbon chain contribute to inhibition of most CYPs, although olivetol on its own is a much weaker inhibitor.**



suggesting CBD is a negative allosteric modulator of CB1 at high doses, meaning it could diminish the effect of THC on CB1.

Furthermore, if the five-carbon side chain (characteristic of CBD) is replaced by a three-carbon group (making the chemical cannabidivarin, CBDV), then the efficiency of this three-carbon ('varin') compound in inhibiting most CYP enzymes is decreased to about 20 percent as well.

Consider the plant cannabinoid tetrahydrocannabivarin (THCV; also shown in figure 1). THCV has shown some promise for increasing insulin sensitivity in type II diabetics, and may be useful as a smoking cessation aid to reduce nicotine craving. Based on the discussion above, THCV will likely be at least 5 times less potent than CBD as a CYP inhibitor, except possibly at CYPs 2C9, 2C19, and 2J2. Overall, THCV seems less likely to cause metabolic drug interactions, unless the dose of THCV required is very large.

## Conclusion

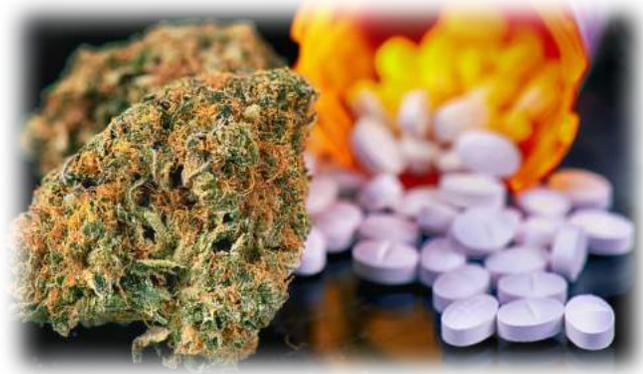
The information presented in this primer is intended to help doctors and patients understand if and when drug interactions with cannabis are likely. It is not meant to stoke fears about drug interactions or add to decades of ill-advised, anti-marijuana hysteria. How dangerous are cannabinoid-drug interactions? As dangerous as mis-dosing the other drugs that a patient is taking. It's a complicated issue, but one doesn't need a firm grasp on all the details of drug interactions to provide cogent guidance to cannabis patients.

Thus far, based on observations regarding the widespread use of raw cannabis flower and full-spectrum cannabis oil, it does not appear that there have been many problems because of cannabinoid-drug interactions. The clinical use of Sativex (a 1:1 CBD:THC sublingual tincture) and Marinol (a pure THC pill) has resulted in few, if any, reported adverse events attributable specifically to interactions with pharmaceuticals.

*To the extent that there have been issues with adverse drug interactions, these have involved high doses of CBD isolates.* Yet it is precisely hemp-derived CBD isolates that proliferate online and in gas stations and food markets throughout the United States. Moreover, CBD isolates, unlike whole-plant extracts, generally require higher doses to be effective. Physicians and patients should be concerned that the current regulatory and legal regime privileges isolates over whole-plant formulations.

Sometimes a blood test may be necessary to see how the concentration of a drug changes—and if a change of dosage is required—when a patient begins taking CBD. This might be the case with chemotherapy, for example, since oncologists often utilize the maximum non-lethal dose to kill cancer cells. If CBD delays the metabolism of a chemotherapy agent, this could result in dangerous levels of a highly toxic drug.

Preclinical research indicates that administering CBD and/or THC in conjunction with first-line chemotherapy drugs could potentiate the latter, thereby reducing the dosage of chemo necessary to treat the cancer. If this indeed translates to human experience, it would be a huge benefit.



***Supplementing opioid-based pain medication with cannabis could result in lower doses of opioids required for adequate pain management.***

Likewise, supplementing an opioid-based pain-management regimen with cannabis could result in lower doses of opioids required for adequate pain relief. Lower doses of opioids will reduce the number of overdose deaths.

There is much more we need to learn about cannabinoid-drug interactions to avoid adverse reactions and harness potential synergies. But this uncertainty is not an excuse for medicine to continue to reject cannabinoid therapies—many pharmaceuticals are incompletely understood.<sup>16</sup> Hopefully, as cannabis therapeutics continues to gain acceptance among physicians and patients, adequate resources will become available for clinical studies involving drug interactions with CBD, THC and other plant cannabinoids.

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<sup>16</sup> See, for example, the label for Cesamet, a pharmaceutical derivative of THC that is approved for treating intractable nausea and vomiting from chemotherapy. “Precise information concerning the metabolites that may accumulate is not available. The relative activities of the metabolites and the parent drug have not been established.” The mechanism of action of common drugs like Tylenol and SSRI antidepressants is also not well established.

# APPENDIX A: GLOSSARY

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## **Allosteric modulation**

A type of protein-chemical interaction. An allosteric modulator changes the shape of the protein, which alters how well another chemical would fit.

## **Anandamide**

The first known endocannabinoid. Discovered by Devane et. al. in 1992.

## **Cannabidiol (CBD)**

A major non-intoxicating plant cannabinoid with significant anti-epileptic and anti-inflammatory properties.

## **7-carboxy-cannabidiol (7-COOH-CBD)**

A major metabolite of CBD which bears some chemical resemblance to the antiepileptic drug valproate.

## **6alpha-hydroxy-cannabidiol (6 $\alpha$ -OH-CBD)**

A minor metabolite of CBD formed when CBD is oxidized by CYPs 3A4, 3A5, 2D6, and 2C19.

## **Cannabidivarin (CBDV)**

A minor plant cannabinoid that has been studied for the treatment of epilepsy and autism-spectrum disorders.

## **Cannabinol (CBN)**

An ostensibly non-psychoactive cannabinoid that is formed when THC degrades in sunlight or heat.

## **Competitive inhibition**

A type of protein-chemical interaction wherein the chemical sits in the active site of the protein, preventing other chemicals from entering.

## **Cytochrome P450 (CYP)**

An important family of enzymes that is involved in metabolizing many pharmaceuticals and endogenous compounds.

## **Epidiolex**

A pharmaceutical formulation of nearly pure CBD that is applied as a sublingual spray.

## **Induction**

A process whereby the activity of an enzyme is increased. Genetic induction refers to changes in gene expression that increase the cell's production of the enzyme.

**K<sub>i</sub>**

A measure of the strength of protein-ligand binding. In this piece, the K<sub>i</sub> indicates the potency with which cannabinoids inhibit CYPs, normalized to the experimental conditions of the study.

**Marinol**

A pharmaceutical formulation of nearly pure THC. Approved by the FDA for treating cancer- and AIDS-related health problems.

**Polycyclic aromatic hydrocarbons (PAHs)**

A class of compounds produced in smoke, whether from cannabis, tobacco, or wood fires.

**Prodrug**

A drug whose metabolites are the primary active compounds.

**Sativex**

A pharmaceutical cannabis extract with a 1:1 ratio of CBD to THC. Approved in many countries outside of the United States

**Terpenes**

Volatile hydrocarbon compounds produced by plants. They are responsible for the smells associated with many plants.

**Tetrahydrocannabinol (THC)**

The major intoxicating plant cannabinoid. It causes a high, alleviates pain, reduces nausea, and is being investigated for numerous other medical conditions.

**11-hydroxy-tetrahydrocannabinol (11-OH-THC)**

Major metabolite of THC. It appears to be more psychoactive than THC itself. It's primarily created by CYP2C9-dependent metabolism of THC.

**11-nor-9-carboxy-tetrahydrocannabinol (11-COOH-THC)**

Major excreted metabolite of THC. It is not psychoactive, and is primarily created by CYP3A4-dependent metabolism of 11-OH-THC.

**Tetrahydrocannabivarin**

A minor plant cannabinoid that has been studied for the treatment of some metabolic and addictive disorders.

## APPENDIX B: K<sub>i</sub> TABLE

Table of K<sub>i</sub> values for cannabinoids' inhibition of various CYP enzymes. The K<sub>i</sub> provides an indication of the potency of inhibition, with smaller K<sub>i</sub>s implying a smaller dose is necessary to cause CYP inhibition. The K<sub>i</sub>s are best used to understand the relative potency of CYP inhibition. The K<sub>i</sub> only suggests the dose of a cannabinoid that causes inhibition—it does not indicate the duration of the effect. It also depends on the second drug used to measure CYP activity.

CYP	THC	CBD	CBN	Reference
1A1	2.87 - 4.78†	0.16†	0.54	Yamaori 2010, Yamaori 2013
1A2	7.54	2.69†	0.08	Yamaori 2010
1B1	2.47	3.63	0.18	Yamaori 2010
2C9	0.94 - 1.50	0.95 - 9.88 <sup>^</sup>	0.88 - 1.29	Yamaori 2012
2C19	1.93	0.79	Not tested	Jiang 2013
3A4	*	1.00	*	Yamaori 2011a
3A5	*	0.20	*	Yamaori 2011a
3A7	*	12.3	*	Yamaori 2011a
2B6	2.81	0.69	2.55	Yamaori 2011b
2B10	Not tested	**	Not tested	Watanabe 2015, Bornheim
2B13	Not tested	**	Not tested	Watanabe 2015, Bornheim
2D6	*	1.16 - 2.69†	*	Yamaori 2011c
2J2	1.06	0.71	0.23	Watanabe 2017

All numbers are K<sub>i</sub>s in μM.

† Cannabinoid was a more potent inhibitor when given before the second drug.

\* K<sub>i</sub> not calculated. Potency notably lower than CBD's potency.

\*\* Only caused induction, not inhibition. In these studies, a fixed dose of 120 mg/kg was used.

<sup>^</sup> The upper bound came from an experiment with a deceased human's liver, which may have had a polymorphism in the CYP2C9 gene. The lower bound used purified enzyme.

# APPENDIX C: ANNOTATED REFERENCES

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## Modulatory Effects

- 48 Comprehensive review of the major CYPs, their substrates, and the factors influencing their function.
- 20 Summary of the role of CYPs in drug metabolism
- 14 A model of heteroactivation with CYP3A4
- 41 This study demonstrates that CBD can decrease CYP3A4 activity in certain circumstances
- 21 This study demonstrates that CBD can increase CYP3A4 activity in certain circumstances
- 6 Suggests that the inductive effects of CBD can counteract its inhibition of CYPs 2C and 3A.
- 7 Demonstrates that animals can develop tolerance to CBD's induction of CYP enzymes.

## Case Report: Warfarin

- 18 Case report on a CBD-warfarin interaction
- 31 Reference on the difficulty of dosing warfarin
- 16 Report of CBD-clobazam interactions in humans

## The CYP1 Family (CYP1A1, 1A2, 1B1)

- 44,47,40 Work on the inhibition of the CYP1 family by cannabinoids.
- 39, 42 Studies suggesting that THC and CBD can induce CYP1A activity or PAH metabolism.

## The CYP2C Family (CYP2C9, 2C19)

- 5 Study demonstrating that THC and its metabolites can induce CYP2C9
- 43 Study on the inhibition of CYP2C9 by cannabinoids
- 21 Inhibition of CYP2C19 by cannabinoids
- 29 CYP2C19 variants
- 30 An article on how CYP2C9 polymorphisms can affect THC metabolism.

## The CYP3A Family (CYP3A4, 3A5)

- 25 A report of vaporized cannabis increasing the metabolism of nelfinavir.
- 41 This study demonstrates that CBD can decrease CYP3A4 activity in certain circumstances
- 9, 32, 36 Studies which indicate that PPAR $\alpha$  can genetically induce CYP3A4 and other CYPs.
- 6 Suggests that the inductive effects of CBD can counteract its inhibition of CYPs 2C and 3A

- 33 A paper presenting methods to predict drug-drug interactions with clobazam.  
16, 17 Report of CBD-clobazam interactions in humans

### **The CYP2B Family (CYP2B1, 2B6, 2B10, 2B13)**

- 6 Demonstration that CBD and one of its metabolites can induce CYP2B10  
37 Demonstration that CBD can induce CYP2B13 activity  
45 Study of cannabinoids inhibiting CYP2B6  
13, 16 CBD-valproate interactions  
4 Study demonstrating limonene and pinene can induce CYP2B.  
12 Myrcene, pinene and limonene can inhibit CYP2B1  
10 Anandamide can induce CYP2B1/2

### **CYP2D6**

- 46 Cannabinoids can inhibit CYP2D6

### **CYP2J2**

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3, 28 CYP2J2's role in eicosanoid metabolism

### **Less Effective or More Dangerous?**

- 7 Tolerance can develop to CBD's inhibition of CYPs  
48 Reviews changes in CYP activity due to inflammation

### **Modes of Administration**

- 19 A review of the bioavailability and pharmacokinetics of THC  
35 Recent data on the pharmacokinetics of high doses of cannabinoids

### **Other Clinical Examples**

- 1 Interactions between vaporized cannabis and opiates  
25 Interactions between cannabis or THC and antiretroviral therapies  
26 CBD-fentanyl interactions  
16, 17 Report of CBD-clobazam interactions in humans

### **Cannabinoid-Cannabinoid Interactions**

- 22, 34 On the metabolism of cannabidiol  
23, 24 Metabolic and physiological interactions between CBD and THC.  
11, 15, 27 Studies indicating synergies in whole-plant extracts that are absent in isolate CBD or THC.

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# ABOUT

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## About the Author

Adrian Devitt-Lee graduated from Tufts University with a MS in Math and a BS in Chemistry in 2016. He is the co-author of several articles in peer-reviewed publications, including the *Journal of Physiology*, *F1000Research*, *SIAM Journal on Applied Mathematics*, and *Physica A*. Devitt-Lee published an earlier report on cannabinoid-pharmaceutical interactions in *Sonoma Medicine*. He has researched cannabis genetics, the interaction between cannabinoids and chemotherapy, and the structure of cannabinoid receptors. As a senior research associate with CannaCraft, Inc., Devitt-Lee provided regulatory input to California government officials on pesticide and solvent safety. He has written numerous articles for Project CBD. Devitt-Lee is currently a research chemist and PhD candidate at the University College of London.

## About Project CBD

Project CBD is a California-based nonprofit dedicated to promoting and publicizing research into the medical uses of cannabidiol (CBD) and other components of the cannabis plant. Project CBD provides educational services for physicians, patients, industry professionals, and the general public. See [www.projectcbd.org](http://www.projectcbd.org) for more information.



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