

## Cannabidiol (CBD) Interactions with Antiepileptic Drugs through Effects on CYP Metabolism

Anti-Epileptic Drug	Effect of CBD on Other Drug		Effect of Other Drug on CBD	
	(1) The Drug Level May Rise	(2) The Drug May Rise and then Fall	(3) CBD Level May Rise	(4) CBD Level May Fall
Alprazolam	Cleared by 3A	N/A	N/A	N/A
Carbamazepine	Cleared by 1A, 2B & 3A	Cleared by 2B	N/A	Speeds Up 2C & 3A
Clobazam*	Cleared by 2B, 2C & 3A	Cleared by 2B	N/A	N/A
Clonazepam	Cleared by 3A	N/A	N/A	N/A
Diazepam	Cleared by 1A, 2B, 2C & 3A	Cleared by 2B	Slows Down 3A	N/A
Ethosuximide	Cleared by 3A	N/A	N/A	N/A
Felbamate	Cleared by 3A	N/A	N/A	Speeds Up 3A
Gabapentin	N/A	N/A	N/A	N/A
Lacosamide	Cleared by 2C	N/A	N/A	N/A
Lamotrigine	N/A	N/A	N/A	N/A
Levetiracetam	N/A	N/A	N/A	N/A
Lorazepam	N/A	N/A	N/A	N/A
Midazolam	Cleared by 2B & 3A	Cleared by 2B	Slows Down 3A	N/A
Oxcarbazepine	N/A	N/A	N/A	Speeds Up 3A
Phenobarbital	Cleared by 2C	N/A	N/A	Speeds Up 2C & 3A
Phenytoin	Cleared by 2C & 3A	N/A	N/A	Speeds Up 2C & 3A
Primidone	Cleared by 2C	N/A	N/A	Speeds Up 2C & 3A
Rufinamide	N/A	N/A	N/A	Speeds Up 3A
Stiripentol	N/A	N/A	Slows Down 3A	Speeds Up 2C & 3A
Temazepam	Cleared by 2B, 2C & 3A	Cleared by 2B	N/A	N/A
Tetrahydrocannabinol	Cleared by 1A, 2C	N/A	N/A	N/A
Topiramate	N/A	N/A	N/A	Speeds Up 3A
Valproic acid	Cleared by 2C	Cleared by 2B (when induced)	Slows Down 3A	N/A
Vigabatrin	N/A	N/A	N/A	N/A
Zonisamide	Cleared by 2C & 3A	N/A	N/A	N/A

# Cannabidiol (CBD) Interactions with Antiepileptic Drugs through Effects on CYP Metabolism

## CBD Effects on Other Drugs (Columns 1 & 2)

(1) CBD can slow down several CYPs, including 1A, 2B, 2C and 3A, so drugs that are cleared by these enzymes can rise to higher levels and have greater effects when CBD is present compared to when it is not. When you add or increase CBD, the effect of the drug can increase, and when you lower CBD, the drug's effect can drop. You can minimize this effect by starting with low doses of CBD, increasing in small steps and separating doses of CBD and these drugs by two hours.

*Examples: alprazolam, clonazepam, ethosuximide, felbamate, lacosamide, phenobarbital, phenytoin, primidone, zonisamide.*

(2) CBD can induce CYP 2B, which amps up its activity and lowers levels of drugs that it is able to clear. So drugs cleared by 2B can drop to lower levels after CBD is added. CBD inhibits 2B activity before it induces it, so drug levels may first rise and then fall when CBD is added. Starting at a low CBD dose can minimize the rise and fall of these drugs, and separating doses of CBD and other drugs by two hours can prevent at least the initial rise.

*Examples: carbamazepine, clobazam, diazepam, midazolam, temazepam, valproic acid.*

\* Clobazam is a special case because CBD affects both it and its active metabolite desmethylclobazam, but in different ways. Clobazam is converted to active metabolite by CYP 2B, 2C and 3A, but the metabolite is made inactive mostly by 2B. CBD can slow 2B, 2C and 3A, so when a person adds CBD to clobazam, breakdown of clobazam and the metabolite both slow down at first. Once CBD induction of 2B kicks in, clobazam converts to active metabolite more quickly than ever, but clearance of the metabolite stays slow. So when CBD is added, levels of clobazam and active metabolite both rise at first, then clobazam goes down while desmethylclobazam rises higher.

To test CBD effects on other drug levels, draw a trough drug blood level both before and four weeks after you add or change CBD, while keeping the dose of the drug the same.

## Effects of Other Drugs on CBD (Columns 3 & 4)

(3) CBD is primarily broken down by CYP 3A, so drugs that slow 3A keep CBD around longer, boosting its effect higher than otherwise. If you are taking one of these drugs and add CBD, your optimal dose of CBD may be lower than when off the drug. Increasing the drug may lower CBD and you may need to increase the CBD dose. On the other hand, if you reduce one of these drugs, you may need to also reduce your CBD dose. Because the drug will inhibit 3A mostly when its level in the liver is high, separating CBD and drug doses by two hours can minimize the impact on CBD.

*Examples: diazepam, midazolam, stiripentol, valproic acid.*

(4) Enzyme CYP 2C can break down CBD, but 3A activity is most important and normally 2C doesn't act on CBD much. The exception is when 2C activity is cranked up by an inducer, in which case 2C can clear CBD rapidly. Inducers of 3A can also cause CBD to be cleared quickly, and some drugs induce both 3A and 2C. The result is that people taking drugs that are inducers may need a higher CBD dose than otherwise. Increasing the drug may reduce CBD, and decreasing the drug can raise the CBD effect. When a CYP enzyme is switched on by an inducer, it can stay switched on even after the drug level falls. So, separating doses of CBD and the drug by two hours may not prevent the amped up clearance of CBD.

*Examples: carbamazepine, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, topiramate.*

(3 & 4) Some drugs can both speed up and slow down clearance of CBD. In this case, inhibition happens first, and CBD may rise, then induction kicks in and takes over, then causing CBD to be broken down more quickly than normal, for as long as the drug is present in the body. *Example: stiripentol.*

To test drug effects on CBD levels, look for a laboratory that tests cannabidiol in serum /plasma (CPT 82542). Draw a trough CBD blood level both before and four weeks after changing the other drug, while keeping the CBD dose the same.

References, including articles cited within these: (1) Zendluka O, et al. 2016. Cannabinoids and cytochrome P450 interactions. *Current Drug Metabolism* 17:1-21. (2) Preissner S, et al. 2010. SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. *Nucleic Acids Res* 38: D237-43.