Interaction of cannabidiol (CBD) with other antiseizure medications (ASMs)

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INTRODUCTION

This narrative literature review investigates pharmacodynamic (PD) & pharmacokinetic (PK) interactions of CBD with ASMs.

METHODS

- Literature search of Cochrane, PubMed & Embase (01/01/15 – 30/04/20)
- Adverse events and side effects were excluded.

RESULTS & DISCUSSION

- 30 studies met criteria
- Interactions between cannabidiol (CBD) and other ASMs are specified in the Table.
- Not all interactions result in ASM concentrations outside therapeutic range. [1]
- CBD inhibits CYP3A4/2C19, which metabolise clobazam (CLB) to its active and inactive metabolites (Figure).
- CBD increases the conc. of the active metabolite of clobazam (N-desmethylclobazam, N-CLB) [2]; effect on efficacy strongly disputed with recent papers refuting this [3].
- Stiripentol also inhibits CYP2C19 & CYP3A4. Stiripentol prevents the CBD-related increase in N-CLB when CLB and CBD are co-prescribed [4].
- Pharmacodynamic interaction between CBD and CLB may occur via the $GABA_A$ receptor [5].
- Increased transaminase levels when valproate and CBD are co-prescribed is not PK, yet may be PD at mitochondria [6].
- Analysis revealed multiple conflicts of interest (expected for studies involving a drug in development).
- Human trials may be unable to detect all PKs; an animal study demonstrated ↑brain conc. of ASMs while serum conc. remained unaltered [7].

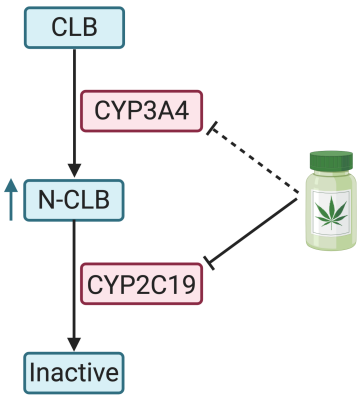

Figure: *CLB metabolism to its active (N-CLB) and inactive metabolites via cytochrome P450 enzymes. CBD inhibits these enzymes, especially CYP2C19. CBD is metabolised by these same enzymes.*

ASM	Highest evidence (nature of interaction)	Discussion	Mechanism
ASMs with evidence for interaction			
Clobazam (CLB)	RCT (PK) Preclin. (PD)	↑ [N-CLB] with CBD. Disputed if [CLB] is affected. Disputed if this contributes to efficacy of CBD [3]. Potentially ↑pts with ↑seizure freq. on CBD than CBD + CLB[8]. ↑ [7-OH-CBD] (active metabolite) with CLB. AE of somnolence may be linked to CBD-CLB PK interaction. PD interaction via $GABA_A$ receptors in preclinical study [5].	PK: CBD inhibiting CYP2C19 , metabolises N-CLB to inactive metabolites [1]. ↑ 7-OH-CBD unclear; may result from CLB inhibition of UGTs or CYPs [18]. PD: $GABA_A$ [5]
Rufinamide	POCS (PK)	↑ [rufinamide] with CBD (14 pts, p<0.01, CBD ≤50 mg/kg/d) [1]. PK interaction may not have therapeutic effect [3]	PK: uncertain – may involve excipient sesamin [1].
Zonisamide	POCS (PK)	↑ [zonisamide] with CBD (14 pts, p=0.02, CBD ≤ 50 mg/kg/d); Only in adult arm of study. [1] PK interaction may not have therapeutic effect [3]	PK: CBD may inhibit CYP3A4, which metabolises zonisamide [1].
Stiripentol (STP)	RCT (PK)	↑ or ↔ [STP] with CBD with CBD [4]. STP blocked ↑[N-CLB] when CBD + CLB [4]. If CBD and CLB have any synergistic activity, which is disputed, this interaction with STP may be of particular relevance.	PK: STP is potent CYP2C19 inhibitor, & so CYP2C19 may be maximally inhibited by STP prior to CBD administration [4].
Sirolimus/ everolimus	ROCS (PK)	↑ [rapamycin inhibitors] with CBD (25 pts, p=0.0003, CBD 5-20 mg/kg/d) and in a case report.	PK: CBD inhibits CYP3A4 which metabolises everolimus.
Esli-carbazepine	POCS (PK)	↑ [eslicarbazepine] with CBD (4 pts, p=0.04, CBD dose ≤50 mg/kg/d [1];1 pt, MCT-oil-based solution CBD) PK interaction may not have therapeutic effect [3]	PK: uncertain – may involve excipient sesamin [1], yet similar result using different formulation.
Brivaracetam	POCS (PK)	↑ [brivacetam] with CBD (POCS with 4 pts, CBD ≤20mg/kg/d [23]; case series of 5 pts).	PK: partly through CBD inhibiting CYP2C19 which metabolises brivaracetam.
Potassium bromide	POCS (PK)	↑ [KBr] with CBD (1 pt, CBD ≤25mg/kg/d)	PK: uncertain
Tiagabine	Preclin. (PK)	Mouse study: ↑ $[tiagabine]_{brain}$ with CBD. ↔ [CBD] with tiagabine [7].	PK: CBD may inhibit CYP3A which metabolises tiagabine. Tiagabine is P-glycoprotein substrate, which CBD inhibits [7].
Gabapentin	Preclin. (PK)	Mouse study: ↑ $[gabapentin]_{serum\ \&\ brain}$ with CBD. ↔ [gabapentin] with CBD [7].	PK: uncertain- potentially brain penetration or kidney elimination [7]
Valproate	Preclin. (PD) RCT (no PK)	↔ [VPA] with CBD (22 pts, CBD ≤50 mg/kg/d) [1]. Repeated by 2 RCTs and 2 POCSs.	PD: ↑ serum transaminases may result from PD at mitochondria.
Leve-tiracetam	Preclin. (PD) RCT (no PK)	↔ [LEV] with CBD (POCS 20 pts, CBD ≤50 mg/kg/d, RCT CBD ≤20 mg/kg/d) [1][4]. ↔ [CBD] with LEV in mouse study [7]. Mouse study: ↓ activity of LEV with CBD (PD) – concerning [7].	PD: uncertain [7].
ASMs where evidence conflicting			
Topiramate	POCSs on PK	RCT: ↔ [topiramate] (unknown pt no.s, CBD ≤20 mg/kg/d) [4] POCS: ↑ [topiramate] with CBD (20pts, CBD ≤50 mg/kg/d) [1] Mouse study: ↑ $[topiramate]_{serum}$ with CBD.↑ $[CBD]_{serum\ \&\ brain}$ with topiramate [7]. PK interaction may not have therapeutic effect [3]	PK: topiramate inhibits CYP2C19 yet induces CYP3A4. Topiramate is P-glycoprotein substrate, which CBD inhibits.
Ox-carbazepine	POCS vs preclin. on PK	POCS: ↔ [oxcarbazepine] with CBD (12pts, CBD ≤50 mg/kg/d) [1] Mouse study: ↑ $[oxcarbazepine]_{serum}$ with CBD. ↑ $[CBD]_{brain}$ with oxcarbazepine [7]	PK: CBD inhibits UGT which conjugates active metabolite of oxcarbazepine. Oxcarbazepine may ↑ brain uptake of CBD [31]
Lacosamide	POCS vs preclin. on PK	POCS: ↔ [lacosamide] with CBD (20pts, CBD ≤50 mg/kg/d) [1]. Mouse study: ↑ $[lacosamide]_{brain}$ with CBD.↑ $[CBD]_{brain}$ with lacosamide [7]. No effect on activity	Mechanism: ↑ penetration of blood brain barrier [7]. Lacosamide inhibits CYP2C19, CYP3A4 & CYP2C9 [7].
Pheno-barbital	POCSs on PK	POCS: ↔ [phenobarbital] with CBD (5pts,CBD≤50 mg/kg/d)[1]. POCS: ↑ [phenobarbital] with CBD (43 to 55 mg/L in 1pt). Mouse study: anticonvulsant effect of CBD not affected by phenobarbital.	PK: phenobarbital is a CYP2C8/9 substrate which CBD inhibits. Phenobarbital induces CYP3A4 & CYP2C19 & so may ↓[CBD].
Pregabalin	POCS vs preclin. on PK	POCS: ↔ [pregabalin] with CBD (2pts, CBD ≤50 mg/kg/d) [6]. Mouse study: ↑ $[CBD]_{brain}$ with pregabalin. ↔ [pregabalin] with CBD [7].	PK: uncertain – pregabalin may ↑ brain uptake of CBD similar to oxcarbazepine [7].
ASMs with evidence against interaction			
Lamotrigine	POCS (no PK)	↔ [lamotrigine] with CBD (30 pts, CBD ≤50 mg/kg/d) [1][7]. Mouse study: ↔ [CBD] with lamotrigine [7].	N/A
Clonazepam	POCS (no PK)	↔ [clonazepam] with CBD (25 pts, CBD ≤50 mg/kg/d) [1].	PK: clonazepam structurally different to clobazam (1,4-benzodiazepine vs 1,5) [1]. Clonazepam metabolites are inactive [1].
Ezogabine	POCS (no PK)	↔ [ezogabine] with CBD (5 pts, CBD ≤50 mg/kg/d) [1].	N/A
Perampanel	POCS (no PK)	↔ [perampanel] with CBD (8 pts, CBD ≤50 mg/kg/d) [1].	N/A
Ethosuximide	POCS (no PK)	↔ [ethosuximide] with CBD (5 pts, CBD ≤50 mg/kg/d) [1].	N/A
Phenytoin	POCS (no PK)	↔ [phenytoin] with CBD (3 pts, CBD ≤50 mg/kg/d) [1].	N/A
Carba-mazepine	POCS (no PK)	↔ [carbamazepine] with CBD (4 pts, CBD ≤50 mg/kg/d) [1].	PK: as carbamazepine induces CYP3A4 & CYP2C19, may ↓[CBD].
Vigabatrin	POCS (no PK)	↔ [vigabatrin] with CBD (3 pts, CBD ≤50 mg/kg/d) [1]	N/A
Midazolam	POCS (no PK)	↔ [midazolam] with CBD (unknown participants, CBD 750mg B.I.D)	PK: ↔ [midazolam] with CBD used to argue CBD has limited effect on CYP3A4
Fenfluramine	POCS (no PK)	↔ [fenfluramine] with CBD (14 recreational drug users, CBD ≤400mg BID [CanniMed Oil 20 CBD:1 THC]).	N/A

POCS = prospective observational cohort study; ROCS = retrospective observational cohort study; RCT = randomised controlled trial; ↔ = no significant change; ↑ = increased; ↓ = decreased; [ASM] = concentration of ASM

CONCLUSION

- PK and PD interactions are present with multiple ASMs, most notably clobazam.
- Larger studies are required to establish how these interactions may influence clinical practice.
- Evidence base currently limited for several ASMs. Clinicians should carefully monitor clinical and laboratory parameters when introducing/altering CBD dosage.

CONCISE REFERENCES

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