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Review

Interaction of cannabidiol with other antiseizure medications: A narrative review

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ABSTRACT

Objective: Cannabidiol is efficacious as an adjunctive treatment in children with epilepsy associated with Dravet and Lennox-Gastaut syndromes. As its role is currently adjunctive, we reviewed the interactions of cannabidiol with other antiseizure medications (ASMs).
Methods: A search of Cochrane, Pubmed and Embase databases from January 2015 to April 2020 was performed. All original research papers discussing interactions between cannabidiol and ASMs were included. Bibliographies of review articles were searched to identify further papers. Adverse events and side effects were excluded.
Results: Cannabidiol interacts with ASMs through both pharmacokinetic and pharmacodynamic mechanisms. Thirty studies were identified (eighteen observational cohort studies, two randomised-control trials, three case reports/series, three animal studies, two briefing reports, an analysis of cohort data and a clinical trial simulation). There is potential for pharmacokinetic interactions between CBD and brivaracetam, clobazam, eslicarbazepine, lacosamide, gabapentin, oxcarbazepine, phenobarbital, potassium bromide, pregabalin, rufinamide, sirolimus/everolimus, stiripentol, tiagabine, topiramate and zonisamide. Pharmacodynamic interactions were identified for clobazam, valproate and levetiracetam. An animal study identified that the brain concentration of ASMs may be altered while the serum concentration remains the same.
Conclusion: Pharmacokinetic and pharmacodynamic interactions exist between cannabidiol and ASMs. The cytochrome p450 system in particular has been implicated in pharmacokinetic interactions, although not exclusively. The existing literature is limited for some ASMs by studies having relatively small cohorts. As increasing numbers of patients use cannabidiol, specialists need to monitor closely for interactions clinically and with blood levels when required.

1. Introduction

Cannabidiol (CBD), a non-psychoactive cannabinoid, is efficacious as an adjunctive treatment in children with epilepsy associated with Dravet (DS) and Lennox-Gastaut syndromes (LGS) [1–6]. Thus, the FDA [7], EMA [8] and NICE [9,10] have licensed highly purified CBD (Epidyolex® or Epidiolex®), with the EMA and NICE specifying this as an option for adjuvant therapy with clobazam in the treatment of DS/LGS. Interactions may influence the efficacy or concentration of medications at their sites of action as well as contribute to side effects and adverse events. With the role of CBD primarily adjuvant, it is important to determine interactions with other antiseizure medications (ASMs).

Interactions may be either pharmacokinetic or pharmacodynamic in nature. Pharmacokinetics describes how the concentration of the drug changes with time, which may be influenced through effects on drug absorption, distribution, metabolism (e.g. through the cytochrome P450 system) or excretion [11]. Pharmacodynamics describes the effects of the drug after binding to its receptor, so may describe interactions at the

Abbreviations: ASM, antiseizure medication; AUCtau, area under plasma concentration-time curve over dosing interval; CBD, cannabidiol; CLB, clobazam; Cmax, maximum plasma drug concentration; EMA, European Medicines Agency; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; LEV, levetiracetam; MDZ, midazolam; NICE, The National Institute for Health and Care Excellence; N-CLB, *N*-desmethylclobazam; OCS, observational cohort study; PD, pharmacodynamic; PK, pharmacokinetic; POCS, prospective observational cohort study; ROCS, retrospective observational cohort study; SRSE, super-refractory status epilepticus; STP, stiripentol; VPA, valproate.

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receptor level, via the signalling pathway, or on the effect of the drug [11]. Pharmacodynamics is therefore a more subjective term: two drugs acting in entirely different pathways yet sharing an outcome may be termed 'pharmacodynamic', for example non-steroidal anti-inflammatories and corticosteroids in reducing inflammation.

This literature review is the first to investigate the pharmacokinetic and pharmacodynamic interactions of cannabidiol with other ASMs. We aim to inform clinicians and identify areas where further research is required. We report key findings for some specific ASMs and highlight shortfalls in the literature at present.

2. Methods

A search of Cochrane, Pubmed and Embase was performed for dates of publication from 1st January 2015 to 30th April 2020. The search term combined "cannab*" with "epil*" or "seiz*" alongside the terms "absorption", "distribution", "protein binding", "tissue binding", "metabolism", "excretion" and "interaction*". All search results were reviewed. For inclusion in this review, search results were required to directly discuss interactions between cannabidiol and other antiseizure medications. This included pharmaceutical / pharmacokinetic interactions, absorption, distribution (protein binding, tissue binding), metabolism (hepatic, nonhepatic), excretion (renal, nonrenal) or pharmacodynamic interactions (direct, indirect). Only original research papers in the English language were selected, including studies involving humans (adult and paediatric populations), animals or laboratory studies. Review bibliographies were searched to identify any further papers. Other cannabinoids under development, not currently of therapeutic use in epilepsy, were not classed as ASM. An adverse event or side effect was not classed as an interaction in this search, as these are not necessarily pharmacokinetic or pharmacodynamic in nature. This search disclosed 354 results on Embase, 312 results on Pubmed and 30 trials in total on Cochrane; 30 of these met selection criteria for this study. Selected results were analysed, with key results and commentary recorded in Table 2 in the Supplementary material. This was re-tabulated for interactions with each ASM in turn in Table 1.

3. Results

Our search revealed thirty studies meeting inclusion criteria. The interactions identified for each antiseizure medication are summarised in Table 1, with critical appraisal of each selected search result included in Table 2 in the Supplementary material. Reports of pharmacokinetic interactions were identified between CBD and brivaracetam, clobazam, eslicarbazepine, lacosamide, gabapentin, oxcarbazepine, phenobarbital, potassium bromide, pregabalin, rufinamide, sirolimus/everolimus, stiripentol, tiagabine, topiramate and zonisamide (Table 1). Of these pharmacokinetic interactions, clobazam, its active metabolite (N-desmethylclobazam, N-CLB), brivaracetam and sirolimus/everolimus have been found to have their serum concentrations altered beyond the therapeutic range [12–16]. Furthermore, Gaston et al., 2019 questioned whether any interactions with rufinamide, eslicarbazepine, zonisamide or topiramate affect treatment response [17]. Pharmacodynamic interactions were identified for clobazam, valproate and levetiracetam.

There is currently no evidence for interactions between CBD and carbamazepine, clonazepam, ethosuximide, ezogabine, fenfluramine, lamotrigine, midazolam, perampanel, phenytoin or vigabatrin. However, this may be a result of firstly small patient cohorts and secondly a lack of investigation: for all apart from lamotrigine, there are no studies investigating how the concentration of CBD or its metabolites may alter with concomitant ASM.

4. Discussion

The complex pharmacology and pharmacokinetics of cannabidiol lends to the possibility of drug interactions. CBD acts through several multifaceted pathways to reduce neuronal excitability. Proposed mechanisms include antagonization at GPR55 receptors, desensitising TRPV1 channels and inhibiting ENT1 adenosine reuptake pumps [18]. The action of CBD potentially extends to further targets, including the 5-HT1A receptor, other TRP channels and even diverse voltage-dependent sodium and potassium channels [19]. The pharmacokinetics of CBD are similarly promiscuous. CBD is metabolised by the cytochrome P450 system, specifically by CYP2C19 to its active metabolite 7-hydroxy-cannabidiol (7-OH-CBD) and then by CYP3A4 to its inactive metabolite 7-carboxy-cannabidiol [20–23]. Other hepatic cytochromes are also capable of metabolising CBD including CYP1A1, CYP1A2, CYP2C9, CYP2D6 and CYP3A5 [22]. Furthermore, CBD inhibits CYP2C19 and CYP3A4 [19]; these interactions are thought to be important contributors to the pharmacokinetic interactions of CBD [24, 19]. However, the relevance of CYP3A4 interactions clinically has been disputed [25–27]. Cytochrome P450 enzymes are not the exclusive route for pharmacokinetic interactions with CBD: CBD has also been shown to inhibit drug transport via *P*-glycoprotein (*P*-gp) [21,28], an ATP-dependent efflux transporter expressed at the intestinal epithelium, hepatocytes, placenta, renal tubular cells, and blood-brain barrier [28].

The strongest evidence basis for an interaction with CBD exists for clobazam (CLB). When the two ASMs are administered in combination, a rise in concentration of the active metabolite of clobazam, N-desmethylclobazam (N-CLB), results [29,30,12,31,1,32,33,25,26,34,20,35, 13]. This is thought to result from a pharmacokinetic interaction through the cytochrome P450 system: CYP3A4 metabolises CLB to N-CLB which in turn is metabolised to inactive metabolites by CYP2C19 [20,36], and CBD inhibits CYP2C19 [12,20,24]. The inhibition of CYP2C19 by CBD is regarded as the basis of the rise in N-CLB concentration [12]. Co-prescription of CLB and CBD has been shown to increase the frequency of side effects experienced by patients, specifically somnolence, sedation and lethargy [7]; the adult arm of Gaston et al., 2017 found an association between the mean level of N-CLB and total frequency of sedation [12]. However this association was not significant in the paediatric cohort, nor across the overall study population [12], limiting interpretation of the relevance of this pharmacokinetic interaction to drug side effects.

The role of the increased concentration of N-CLB in the efficacy of CBD has been much debated. Early prospective observational cohort studies identified a higher treatment response to CBD in patients receiving clobazam [37–39], and a recent clinical trial simulation concluded that the reduction of median drop seizure frequency observed in the CBD trial GWPCARE3 may be explained by a rise in N-CLB concentration [40]. However, there is significant evidence to the contrary. An abstract pooling data from the GWPCARE3 and 4 trials by Thiele et al., 2017 noted responses to CBD were independent of whether patients were co-prescribed clobazam [41]. Two recent studies by Savage et al., 2019 and Gaston et al., 2019 have further investigated this question [17,35]. Savage et al., 2019 retrospectively analysed data from 47 patients, and found that after two months of treatment, at the best point of seizure control, there was no significant difference in the mean reduction in weekly seizure frequencies between patients receiving clobazam and those not [35]. They only identified a weak, non-significant correlation between N-CLB concentration and reduction

Table 1
Antiseizure medication interactions with cannabidiol.

Antiseizure medication	Highest evidence (nature of interaction)	Effect of CBD on ASM pharmacokinetics	Effect of ASM on CBD pharmacokinetics	Pharmacodynamic interaction	Therapeutic effect of interaction	Mechanism
ASMs with either unanimous or conflicting evidence for interaction						
Brivaracetam	POCS (PK)	↑ [brivacetam] with CBD (POCS with 4 pts, CBD ≤ 20 mg/kg/d [13]; case series of 5 pts [15]).	No studies investigating [CBD] with brivaracetam.	N/A	Change in [brivacetam] may be outside therapeutic range [13,15].	Partly through CBD inhibiting CYP2C19 which metabolises brivaracetam [15].
Clobazam (CLB)	RCT (PK) Preclinical (PD)	↑ [N-CLB] with CBD in OCSs [29,30,12,31,25,26,34,20,35,13] and a RCT [1,32,33]. This rise was variable and most commonly significant. [CLB] may ↓ [12], not be affected in a statistically significant manner [29,30,1,25,26,20], or ↑ [46,34]. The SEs of somnolence, sedation and lethargy observed when CLB and CBD are co-prescribed [7] have been associated with ↑ mean [N-CLB] [12]. This was only significant in the adult arm of this study [12].	↑ [7-OH-CBD] (active metabolite) with CLB [31,25,26,34,20]. ↑ [CBD] with CLB reported [25,26,34], yet disputed [20].	PD interaction via $GABA_A$ receptors in preclinical study [24].	Disputed if CLB contributes to efficacy of CBD: recent studies argue CBD efficacy independent of CLB [17,35] (see main text). Potentially more pts with worsening of seizures on CBD alone than CBD + CLB [7,42].	PK: CBD inhibiting CYP2C19, which in turn metabolises N-CLB to inactive metabolites [12]. Mechanism for rise in 7-OH-CBD not determined, yet may result from CLB inhibition of UGTs or CYP enzymes [20]. PD: $GABA_A$
Eslicarbazepine	POCS (PK)	↑ [eslicarbazepine] with CBD [12] (4 pts, p = 0.04, CBD dose ≤50 mg/kg/d, mean change within therapeutic range [12]; 1 pt, MCT-oil-based solution CBD [13])	No studies investigating [CBD] with eslicarbazepine.	N/A	Mean ↑ [eslicarbazepine] within therapeutic range [12]. PK interaction may not have therapeutic effect - no difference between pts on any of rufinamide, eslicarbazepine, zonisamide or topiramate (+ CBD) with pts receiving none [17].	Uncertain – may involve excipient sesamin [12], yet this questioned by similar result when different formulation used [13].
Gabapentin	Preclinical (PK)	Mouse study: ↑ $[gabapentin]_{serum\ \&\ brain}$ with CBD.	Mouse study: ↔ [gabapentin] with CBD [21].	Mouse study: CBD ↑ activity of gabapentin (may however be at least in part a result of PK interactions) [21].	Mouse study: CBD ↑ activity of gabapentin [21].	Uncertain- may be attributed to brain penetration or kidney elimination (gabapentin not bound by plasma proteins or metabolised by CYPs, & is excreted as unchanged drug) [21]
Lacosamide	Conflicting POCS with preclinical (PK for CBD on lacosamide). Preclinical (PK for lacosamide on CBD).	POCS: ↔[lacosamide] with CBD (20pts, CBD ≤ 50 mg/kg/d [12]). Mouse study: ↑$[lacosamide]_{brain}$ with CBD [21].	Mouse study: ↑ $[CBD]_{brain}$ with lacosamide [21].	Mouse study: no effect of CBD on lacosamide activity.	Mouse study: no effect of CBD on lacosamide activity.	May be ↑ penetration of blood brain barrier by CBD & lacosamide [21]. Lacosamide inhibits CYP2C19, CYP3A4 & CYP2C9 [21].
Levetiracetam	Preclinical (PD) RCT (no PK)	↔ [LEV] with CBD (POCS 20 pts, CBD ≤ 50 mg/kg/d [12]; RCT CBD ≤ 20 mg/kg/d [1]).	Mouse study: ↔ [CBD] with LEV [21].	Mouse study: ↓ activity of LEV with CBD (PD) – concerning [21].	Unknown	PD: uncertain [21].
Oxcarbazepine	Conflicting POCS with RCT (PK for CBD on oxcarbazepine). Preclinical (PK for CBD on oxcarbazepine)	POCS: ↔ [oxcarbazepine] with CBD (12pts, CBD ≤ 50 mg/kg/d [12]) Mouse study: ↑ $[oxcarbazepine]_{serum}$ with CBD [21].	Mouse study: ↑ $[CBD]_{brain}$ with oxcarbazepine [21]	Mouse study: CBD ↑ activity of oxcarbazepine (may however be at least in part a result of PK interactions) [21].	Mouse study: CBD ↑ activity of oxcarbazepine [21].	CBD inhibits UDP-glucuronyl transferase which conjugate active metabolite of oxcarbazepine. Oxcarbazepine may ↑ brain uptake of CBD [21]
Phenobarbital	Conflicting POCS (PK for CBD on phenobarbital)	POCS: ↔ [phenobarbital] with CBD (5pts, CBD ≤ 50 mg/kg/d [12]). POCS: ↑ [phenobarbital]	No studies investigating [CBD] with phenobarbital.	Mouse study: anticonvulsant effect of CBD not affected by phenobarbital [47].	Mouse study: anticonvulsant effect of CBD not affected by phenobarbital [47].	Phenobarbital is a CYP2C8/9 substrate which CBD inhibits [48]. Phenobarbital

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Table 1 (*continued*)

Antiseizure medication	Highest evidence (nature of interaction)	Effect of CBD on ASM pharmacokinetics	Effect of ASM on CBD pharmacokinetics	Pharmacodynamic interaction	Therapeutic effect of interaction	Mechanism
		with CBD (↑[phenobarbital] from 43 to 55 mg/L in 1 pt, CBD ≤25 mg/kg/d [46])				induces both CYP3A4 & CYP2C19 & so theoretically may ↓ [CBD] [48]
Potassium bromide	POCS (PK)	↑ [KBr] with CBD (1 pt, CBD ≤25 mg/kg/d [46]).	No studies investigating [CBD] with potassium bromide.	N/A	In 1 pt recorded, rise in [KBr] was 21 %.	Uncertain [46].
Pregabalin	Preclinical (PK)	↔ [pregabalin] with CBD (2pts, CBD ≤ 50 mg/kg/d [12]). Mouse study: ↔ [pregabalin] with CBD [21].	Mouse study: ↑ $[CBD]_{brain}$ with pregabalin [21].	Mouse study: CBD ↑ activity of pregabalin (may however be at least in part a result of PK interactions) [21].	Mouse study: CBD ↑ activity of pregabalin [21].	Uncertain – pregabalin may ↑ brain uptake of CBD similar to oxcarbazepine [21].
Rufinamide	POCS (PK)	↑ [rufinamide] with CBD (14 pts, $p < 0.01$, CBD ≤ 50 mg/kg/d, mean change within therapeutic range [12]).	No studies investigating [CBD] with rufinamide.	N/A	Mean ↑ [rufinamide] within therapeutic range [12]. PK interaction may not have therapeutic effect - no difference between pts on any of rufinamide, eslicarbazepine, zonisamide or topiramate (+ CBD) with pts receiving none [17].	Uncertain – may involve excipient sesamin [12].
Sirolimus/ everolimus	ROCS (PK)	↑ [rapamycin inhibitors] with CBD (25 pts, $p = 0.0003$, CBD 5-20 mg/kg/d [14]; 1 pt CBD ≤ 20.4 g/kg/day [16]).	No studies investigating [CBD] with sirolimus/ everolimus.	N/A	Increase was statistically significant ($p = 0.0003$) & in some patients the trough level of mTOR inhibitor doubled or tripled with CBD [14]. Dramatic ↑[everolimus] in case report [16].	CBD may inhibit CYP3A4, which metabolises everolimus [14]
Stiripentol (STP)	RCT (PK)	↑[STP] with CBD (unknown cohort, CBD ≈20 mg/kg/d [25,26]; 12 pts, CBD ≤ 20 mg/kg/d [20]) or ↔ [STP] with CBD (unknown cohort, CBD ≤ 20 mg/kg/d [1]) (RCT). STP blocked ↑[N-CLB] when CBD + CLB [1]. If CBD and clobazam have any synergistic activity, which is disputed, this interaction with STP may be of particular relevance.	STP may ↓ [7-OH-CBD] and ↓[7-COOH-CBD] (12 pts, CBD ≤ 20 mg/kg [20]), although this is disputed (unknown cohort, CBD ≈20 mg/kg/d [25,26]).	N/A	Authors concluded direct interaction between STP & CBD unlikely to be clinically relevant [20]. STP effect on [CBD] not powered for statistical significance [20]. If CBD and CLB have therapeutic synergy, STP may theoretically influence this.	↑[STP] may result from CBD inhibition of CYP2C19 [20]. STP is metabolised by CYP2C19. CYP3A4 & CYP1A2 and inhibits both CYP3A4 and 2C19 [49] Prevention of ↑[N-CLB] may result from maximal inhibition of CYP2C19 by STP prior to CBD administration [1]. Mechanism for ↓[CBD metabolites] unknown [20].
Tiagabine	Preclinical (PK)	Mouse study: ↑ $[tiagabine]_{brain}$ with CBD [21].	Mouse study: ↔ [CBD] with tiagabine [21].	Mouse study: CBD ↑ activity of tiagabine (may however be at least in part a result of PK interactions) [21].	Mouse study: CBD ↑ activity of tiagabine [21].	CBD may inhibit CYP3A which metabolises tiagabine. Tiagabine is *P*-glycoprotein substrate which CBD inhibits [21]
Topiramate	Conflicting POCS with RCT (PK for CBD on topiramate). Preclinical (PK for topiramate on CBD)	RCT: ↔ [topiramate] (unknown cohort, CBD ≤ 20 mg/kg/d [1]) POCS: ↑ [topiramate] with CBD (20pts, CBD ≤ 50 mg/kg/d, mean change within therapeutic range [12]) Mouse study: ↑ $[topiramate]_{serum}$ with CBD	Mouse study: ↑ $[CBD]_{serum\ \&\ brain}$ with topiramate [21].	Mouse study: CBD ↑ activity of topiramate (may however be at least in part a result of PK interactions) [21].	Human and mouse study conflict. Mouse study: CBD ↑ activity of topiramate [21]. POCS: no difference between pts on any of rufinamide, eslicarbazepine, zonisamide or	Topiramate inhibits CYP2C19 [21] yet induces CYP3A4 [48]. Topiramate is P-glycoprotein substrate, which CBD inhibits.

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Table 1 (*continued*)

Antiseizure medication	Highest evidence (nature of interaction)	Effect of CBD on ASM pharmacokinetics	Effect of ASM on CBD pharmacokinetics	Pharmacodynamic interaction	Therapeutic effect of interaction	Mechanism
		[21]. The higher pt cohort in POCS vs RCT (& so potentially greater power), or the higher CBD dose used may explain their discrepancy.			topiramate (+ CBD) with pts receiving none [17]	
Valproate	Preclinical/ briefing (PD) RCT (no PK for CBD on [VPA]) POCS (PK for VPA on [7-COOH-CBD])	↔ [VPA] with CBD (22 pts, CBD ≤ 50 mg/kg/d [12]). Repeated by 2 RCTs [1,44,50] and 2 POCSs [25,26,20]. Plasma C_{max} & AUC_{tau} of VPA & metabolite 2-propyl-4-pentenoic acid ↓ with CBD in one of these RCTs [44,50], yet ratio point estimates were similar to placebo. Neither CBD or 7-COOH-CBD affected plasma protein binding (PPB) of VPA [44,50].	↔ [CBD] with VPA (unknown cohort, CBD ≈20 mg/kg/d [25,26]; 12 pts, CBD ≤ 20 mg/kg/d [20]). Slight ↑ [7-COOH-CBD] with VPA reported [18] yet disputed [25,26]. VPA did not affect PPB of CBD or 7-COOH-CBD [44,50].	↑ serum transaminases may result from PD interaction at mitochondria [45]. Rat study noted ↑efficacy when CBD + valproate co-prescribed [47]. Serum drug conc.s not recorded & published as abstract - cannot determine if represents a therapeutic PD interaction.	Where identified, authors still believed rise in ↑ [7-COOH-CBD] unlikely to be clinically relevant [20]. ↑ serum transaminases must be monitored.	PD: Unclear – may involve interaction at mitochondria [45]. PK: valproate is a UGT1A9/2B7 substrate, which CBD inhibits [48].
Zonisamide	POCS (PK)	↑ [zonisamide] with CBD (14 pts, p = 0.02, CBD ≤ 50 mg/kg/d, mean change within therapeutic range [12]). Only in adult arm of study; [zonisamide] positively correlates with age [51,12]	No studies investigating [CBD] with zonisamide.	N/A	Mean ↑ [zonisamide] within therapeutic range [12]. PK interaction may not have therapeutic effect - no difference between pts on any of rufinamide, eslicarbazepine, zonisamide or topiramate (+ CBD) with pts receiving none [17].	CBD may inhibit CYP3A4, which metabolises zonisamide [12].
ASMs with no evidence currently for interaction						
Carbamazepine	POCS (no PK)	↔ [carbamazepine] with CBD (4 pts, CBD ≤ 50 mg/kg/d [12]).	No studies investigating [CBD] with carbamazepine.	N/A	N/A	Theoretically, as carbamazepine induces both CYP3A4 and CYP2C19, it may ↓[CBD] [48]
Clonazepam	POCS (no PK)	↔ [clonazepam] with CBD (25 pts, CBD ≤ 50 mg/kg/d [12]).	No studies investigating [CBD] with clonazepam.	N/A	N/A	Clonazepam is structurally different to clobazam (1,4-benzodiazepine vs 1,5-benzodiazepine) which may account for differences [12]. Clonazepam metabolites are inactive regardless of any change [12].
Ethosuximide	POCS (no PK)	↔ [ethosuximide] with CBD (5 pts, CBD ≤ 50 mg/kg/d [12]).	No studies investigating [CBD] with ethosuximide.	N/A	N/A	N/A
Ezogabine	POCS (no PK)	↔ [ezogabine] with CBD (5 pts, CBD ≤ 50 mg/kg/d [12]).	No studies investigating [CBD] with ezogabine.	N/A	N/A	N/A
Fenfluramine	POCS (no PK)	↔ [fenfluramine] with CBD (14 recreational drug users, CBD ≤400 mg BID [CanniMed Oil 20 CBD:1 THC] [52]), although PKs of fenfluramine affected in a non-statistically significant manner [52].	No studies investigating [CBD] with fenfluramine.	N/A	N/A	N/A

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Table 1 (*continued*)

Antiseizure medication	Highest evidence (nature of interaction)	Effect of CBD on ASM pharmacokinetics	Effect of ASM on CBD pharmacokinetics	Pharmacodynamic interaction	Therapeutic effect of interaction	Mechanism
Lamotrigine	POCS (no PK)	↔ [lamotrigine] with CBD (30 pts, CBD ≤ 50 mg/kg/d [12]) Mouse study: ↔ [lamotrigine] with CBD [21].	Mouse study: ↔ [CBD] with lamotrigine [21].	Mouse study: ↔ activity of lamotrigine with CBD.	N/A	N/A
Midazolam	POCS (no PK)	↔ [midazolam] with CBD (unknown participants, CBD 750 mg B.I.D [25,26]).	No studies investigating [CBD] with midazolam.	N/A	N/A	The absence of an observed effect by CBD on midazolam has been used to argue that CBD has limited clinical effect on CYP3A4 [25,26].
Perampanel	POCS (no PK)	↔ [perampanel] with CBD (8 pts, CBD ≤ 50 mg/kg/d [12]).	No studies investigating [CBD] with perampanel.	N/A	N/A	N/A
Phenytoin	POCS (no PK)	↔ [phenytoin] with CBD (3 pts, CBD ≤ 50 mg/kg/d [12]).	No studies investigating [CBD] with phenytoin.	N/A	N/A	N/A
Vigabatrin	POCS (no PK)	↔ [vigabatrin] with CBD (3 pts, CBD ≤ 50 mg/kg/d [12])	No studies investigating [CBD] with vigabatrin.	N/A	N/A	N/A

[ASM] = concentration of ASM; OCS = observational cohort study; PD = pharmacodynamic; PK = pharmacokinetic; POCS = prospective observational cohort study; Pt = patient; RCT = randomised controlled trial; ROCS = retrospective observational cohort study; SE = side effect; ↔ = no significant change; ↑ = increase; ↓ = decrease.

in weekly seizure frequency [35]. Gaston et al., 2019 conducted a larger prospective study of 132 participants, and even using a maximum dose of 50 mg/kg/day CBD, there was no significant difference in seizure frequency or severity reduction between those receiving clobazam and those not after 12 weeks [17].

A pharmacodynamic interaction between CBD and clobazam has also been recently proposed to occur through the $GABA_A$ receptor, with this demonstrated in a mouse model to enhance efficacy [24]. Interestingly, this study showed that a sub-anticonvulsant dose of CBD did not promote greater anticonvulsant effects despite increasing plasma clobazam concentrations; however N-CLB concentrations were not recorded in this particular experiment [24]. The authors conclude that although there may be synergistic action through $GABA_A$, the enhanced anticonvulsant effect of CBD and CLB in combination is likely multimodal, involving distinct mechanisms of action such as CBD acting at GPR55 [24]. What is not often considered is whether clobazam increasing the concentration of 7-OH-CBD may also contribute to efficacy [20]. It should be noted that there have been concerns raised regarding the safety of CBD administration without concomitant CLB [42]: clinical trials have demonstrated a greater proportion of patients experience a worsening of seizure frequency when prescribed CBD without CLB [7,42]. An analysis on the safety of CBD is beyond the scope of this review, however further research into this would be prudent.

Co-prescription of CBD with valproate is well-known to produce a rise in transaminases [43]. This however does not occur through a pharmacokinetic alteration in valproate or CBD concentrations [12,1,32,44,25,20]. The FDA proposed that this may result from a pharmacodynamic interaction in mitochondria [45]. A slight increase in concentration of a metabolite of CBD (7-COOH-CBD) has been observed with valproate administration [20], yet has been disputed [25,26]. This is not thought to be of clinical relevance [20].

There is debate as to whether a pharmacokinetic interaction exists between CBD and topiramate. No alterations in serum concentration of topiramate were found in a randomised controlled trial [1], while they were identified in an open-label trial [12]. A mouse study supports evidence for an interaction [21] and discussed plausible underlying mechanisms, e.g. through CBD inhibiting *P*-glycoprotein and so reducing renal or bile excretion of topiramate. Topiramate was in turn shown to elevate serum and brain concentrations of CBD in this study, potentially through inhibition of CYP2C19 [21].

The pharmacokinetics of stiripentol may be affected by CBD [25,20], although this is disputed [1]. Whether stiripentol alters the concentration of CBD is similarly debated [25,26,20], although this would be likely not be of clinical relevance. A randomised controlled trial demonstrated that stiripentol blocks a rise in N-desmethylclobazam caused by CBD with clobazam [1], which may result from stiripentol being both metabolised by and inhibiting CYP2C19 and CYP3A4, the same enzymes CBD interacts with. If, although disputed, the rise in concentration of N-desmethylclobazam contribute to the efficacy of CBD [40,24], it may be extrapolated that stiripentol may affect this. Further investigations are required to inform clinical practice.

Although no pharmacokinetic interactions have been identified with levetiracetam, a mouse study identified that CBD at a dose of 100 mg/kg decreased the antiseizure activity of levetiracetam against 6 Hz-induced psychomotor seizure [21]. Neither levetiracetam nor CBD were reduced in serum concentration when co-administered, suggesting this to be pharmacodynamic in nature [21]. Although this interaction is concerning, it must be noted that this dose was significantly higher than what is clinically prescribed at present. This pharmacodynamic interaction has not been investigated in human studies either. This same mouse study identified increases in the activity of multiple ASMs (topiramate, oxcarbazepine, pregabalin, tiagabine, and gabapentin) upon the addition of CBD [21], however none of these could be classified as purely pharmacodynamic interactions, as pharmacokinetic alterations were simultaneously detected. Regardless, this is an example of the term pharmacodynamic indicating a therapeutic benefit of two medications used in combination, and so may not in fact indicate interactions at

either receptors or signalling pathways.

Analysis of the literature revealed a paucity of studies investigating the effect of ASMs on the pharmacokinetics of CBD. Furthermore, the evidence base for some ASM interactions was remarkably small, e.g. for eslicarbazepine the total patient cohort was only five [12]. Comparison between studies is complicated by varied trial durations: a time delay may be required for interactions based on altered enzyme expression to occur. There appears no consensus on how long patients ought to be investigated for all interactions to manifest.

A further difficulty for investigating interactions is that an excipient in the formulation of Epidyolex® may interact with ASMs, with Gaston et al., 2017 reporting that sesamin may influence interactions for rufinamide [12]. Additionally, human trials may be unable to detect all pharmacokinetic interactions; an animal study demonstrated elevations in the brain concentration of tiagabine while its serum concentrations remained unaltered [21]. There may therefore be pharmacokinetic interactions altering brain ASM concentrations in patients, which cannot be readily detected. Although animal studies provide the opportunity to detect such interactions, there is difficulty in comparing mouse and human studies directly due to differences in the cytochrome P450 systems. Our analysis also revealed multiple conflicts of interest in this field, although the extent of this varied. This is partly expected for studies discussing a drug under development, yet must be kept in consideration when analysing the literature.

5. Conclusions

Cannabidiol (CBD) interacts both pharmacokinetically and pharmacodynamically with multiple antiseizure medications, most notably with clobazam. Pharmacodynamic interactions have been detected between CBD and clobazam, valproate and levetiracetam, and there are reports of pharmacokinetic interactions for brivaracetam, clobazam, eslicarbazepine, lacosamide, gabapentin, oxcarbazepine, phenobarbital, potassium bromide, pregabalin, rufinamide, sirolimus/everolimus, stiripentol, tiagabine, topiramate and zonisamide. These interactions do not all affect therapeutic action. For many of these ASMs further larger studies are required to determine how these interactions influence clinical practice. Additional interactions may be present with other ASMs where the current evidence base for no interaction is small; this is particularly the case regarding whether ASMs affect the pharmacokinetics of CBD. As the evidence is currently limited for a number of ASMs, clinicians should carefully monitor both clinical and laboratory parameters when introducing or changing CBD dosage, whichever ASM the patient is receiving.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.09.010.

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