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REVIEW

Cannabidiol drug interaction considerations for prescribers and pharmacists

Myfanwy Graham[a,b], Jennifer H Martin[a,b], Catherine J Lucas[a,b], Bridin Murnion[c] and Jennifer Schneider[a,b]

[a]Australian Centre for Cannabinoid Clinical and Research Excellence, Newcastle, Australia; [b]Centre for Drug Repurposing & Medicines Research, School of Medicine and Public Health, the University of Newcastle, Australia; [c]Discipline of Addiction Medicine, University of Sydney, Australia

ABSTRACT

Introduction: In light of the widespread use of non-prescribed and prescribed cannabidiol, the use of cannabidiol with other medications is likely, and this may result in drug interactions.

Areas covered: We aimed to ascertain if clinical guidance could be provided on the dose range at which cannabidiol drug interactions are likely to occur with concurrently prescribed medicines. Literature searches were conducted in Embase, MEDLINE, and PubMed from database inception to January 2022 using Emtree and MeSH terms. Reference list screening yielded further studies. Using currently available data, likely drug interactions of which prescribers of cannabidiol need to be aware, at the doses likely to cause clinically significant interactions, and drug dosing changes that may be needed are highlighted.

Expert opinion: We have provided an overview of evidence-based pharmacokinetic predictions and general guidance about the dose range at which clinically relevant cannabidiol drug interactions are likely. For an individual patient, there are inherent limitations in providing clinical guidance due to gaps in specific drug dose–response data and knowledge of individual pharmacokinetic profiles, including different co-morbidities, and concurrent medicines. Clinician awareness of cannabinoid pharmacology, along with clinical and therapeutic drug monitoring, are current best practice approaches to manage cannabinoid drug interactions.

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Medicinal cannabis; cannabidiol; pharmacokinetics; drug interactions; review

1. Introduction

Internationally, cannabidiol is becoming more readily available to consumers via prescription and/or in the absence of a prescription. The wide range of indications for which use of cannabidiol is promoted means that patients on cannabidiol are likely to be coadministering other medicines. With underpinning knowledge on drug–drug interactions usually provided through early phase clinical studies missing, data on clinically relevant interactions to inform prescribers and consumers is lacking. This narrative review aims to assist clinicians by providing an overview of the pharmacokinetics of cannabidiol, potential mechanisms of drug–drug interactions and a summary of data on drug–drug interactions from in vitro studies, animal studies, real-world case reports and clinical studies. Although general awareness of drug interactions is available in regulatory guidance for registered cannabinoids, the manuscript helps guide prescribers to select doses of cannabinoids where likely drug interactions can be managed.

2. Methods

2.1. Literature search

Literature searches from database inception to January 2022 were conducted in Embase, MEDLINE, and PubMed databases, using Emtree and MeSH terms. Search terms included 'cannabidiol,' 'drug interaction(s)', and 'pharmacokinetics.' The search was limited to articles published in English language. A focus on the cannabinoid cannabidiol was a key inclusion criterion. Literature based on cannabinoids other than cannabidiol were excluded. Reference lists of articles retrieved were manually screened for additional studies. Following deduplication of retrieved articles in EndNote, all articles were independently screened by two authors and a consensus on included articles was reached.

3. Results

3.1. Pharmacokinetics of clinical doses

3.1.1. Absorption

Cannabidiol has low and variable oral bioavailability, due predominantly to its low aqueous solubility and extensive first-pass metabolism [1]. A model-based analysis of the oral cannabidiol dose–exposure relationship and bioavailability concluded that systemic exposure did not increase proportionally with oral doses of 750 mg and above, and bioavailability, estimated to be 6.5% at 3000 mg, decreased with increasing dose [2]. Administering oral cannabidiol with a high-fat meal increases the peak plasma cannabidiol concentration (Cmax) and area under the plasma cannabidiol concentration–time curve (AUC). In subjects receiving a single oral 750 mg cannabidiol dose in the fasted state, and with a high-fat meal, the

CONTACT Myfanwy Graham Myfanwy.graham@newcastle.edu.au Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE), Division of Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

Article highlights

- The rapid uptake of non-prescribed and prescribed cannabidiol use increases the likelihood of potential interactions with other medications.
- The article provides an overview of cannabidiol drug interaction literature.
- The concept of a dose-threshold for cannabidiol drug interactions is explored.
- Clinical guidance for prescribers on cannabidiol drug interactions is provided, including quick reference summary tables.
- Gaps in existing knowledge and research are highlighted.

geometric mean Cmax increased from 187 to 1050 ng/mL, and AUC $_{0-\infty}$ was 3.8 times higher with food [3]. Administration of a medium-range dose of 300 mg (or 200 mg in one subject) with a high fat/calorie meal increased the Cmax by an average of 14-fold (from 9 to 126 ng/mL), and there was a fourfold increase in AUC $_{0-\infty}$ [4].

The formulation of the oral cannabidiol product also significantly affects plasma cannabidiol concentration and AUC. In a study where 16 subjects received a single 25 mg oral dose of cannabidiol of a self-emulsifying drug delivery system (SEDDS) or oil formulation in a fasted state, the mean Cmax observed was 13.53 ng/mL with the SEDDS formulation compared to 3.05 ng/mL for the oil formulation. The AUC (0–8 h) for the SEDDs formulation was 2.85 times higher than the oil formulation [1].

Following inhalation or smoking of cannabidiol, peak plasma cannabidiol concentrations occur within minutes. Smoked cannabidiol was observed to have an average bioavailability of 31%, which is higher than that observed for oral cannabidiol [5]. A study comparing the pharmacokinetics of 2.1 mg inhaled cannabidiol and 50 mg oral cannabidiol reported a mean Cmax of 18.78 ng/mL for inhaled and 6.3 ng/mL for oral cannabidiol. In a study investigating cannabidiol delivered via a dry powder inhaler, the dose-adjusted mean AUC for inhaled cannabidiol was approximately nine times higher than oral cannabidiol [6].

3.1.2. Distribution

Due to its high lipophilicity, cannabidiol is extensively distributed with rapid distribution into the brain, adipose tissue, and other organs. With chronic administration, cannabidiol may accumulate in adipose tissue and may slowly release from this depot [5,7]. Cannabidiol is >80% protein-bound, and similar protein binding was observed in patients with normal and impaired renal function [8]. A trend toward increased fraction unbound in the presence of hepatic impairment was observed, although authors noted difficulties in assaying the unbound cannabidiol fraction [9].

3.1.3. Elimination

Following oral administration, cannabidiol undergoes extensive first-pass metabolism. Cannabidiol is primarily metabolized by CYP2C19 and CYP3A4. Other CYP enzymes, including CYP2C9, CYP2D6 may also play a role [10]. Cannabidiol is also subject to Uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT) dependent glucuronidation by UGT enzymes and is a substrate of UGT1A7, UGT1A9, and UGT2B7 enzymes [11].

When deuterium-labeled cannabidiol was administered intravenously (IV), a large proportion of cannabidiol was observed to be excreted unchanged in the feces. A suggested mechanism for transport into the bile is by canalicular efflux transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and/or multi-drug resistance associated protein 2 (MRP2) [12].

Pharmacokinetic studies using oral formulations report clearance (CL) values as CL/F, where F is the bioavailability. Since cannabidiol bioavailability is low, CL/F values reported are large. Using an absolute bioavailability of 6% for oral cannabidiol, the estimated CL of cannabidiol is likely to be around 67 L/h. Perucca and Bialer [13] observed that this estimate is close to that reported for deuterium labeled IV cannabidiol. Based on this, cannabidiol may behave as a high clearance drug and this has implications when predicting the magnitude of drug–drug interactions [13].

Since hepatic metabolism plays an important role in the elimination of cannabidiol, hepatic impairment is likely to influence the plasma cannabidiol concentrations. In a phase I study, where a single oral dose of 200 mg cannabidiol was administered to subjects with normal and different degrees of hepatic impairment, cannabidiol AUC was slightly higher with mild impairment, and clinically relevant increases were observed with moderate and severe hepatic impairment. The mean geometric Cmax in subjects with normal hepatic function and moderate and severe hepatic impairment was 148 ng/mL, 354 ng/mL and 381 ng/mL, respectively [9].

Impairment of renal function did not produce significant changes in Cmax or AUC following a single oral 200 mg dose [8].

3.2. Mechanisms of pharmacokinetic drug–drug interactions

Pharmacokinetic drug–drug interactions may occur in the absorption, distribution and elimination stages and result in increased or decreased plasma drug concentrations. When cannabidiol is co-administered with another drug, cannabidiol may affect the pharmacokinetics of the other drug and the pharmacokinetics of cannabidiol may also be affected by a co-administered drug.

A common mechanism of drug–drug interaction is the induction or inhibition of enzymes involved in drug metabolism. CYP450 enzymes are involved in the metabolism of many drugs, including cannabidiol. UGT enzymes also represent an important pathway of metabolism. Genetic polymorphisms occur in CYP450 enzymes, including CYP3A4, CYP2D6, CYP2C9 and CYP2C19, which have been reported to be involved in cannabidiol metabolism. Patients may be ‘poor metabolizers’ and others ‘ultra metabolizers’ and genetic variation can markedly alter the severity of drug–drug interactions [14,15]. An in vitro study recently observed that the formation of the active metabolite 7-hydroxy-cannabidiol (7-OH-CBD) was positively correlated with CYP2C19 activity but not associated with CYP2C19 genotype [16].

Drug transporters present in the liver, kidney, blood–brain barrier and intestine are involved in the absorption, distribution and elimination of some drugs. Efflux transporters include P-gp, MRP2, and BCRP. Genetic polymorphism and the inhibition or induction of these transporters by one drug may result in changes in plasma drug concentrations of another drug [14].

3.3. In vitro studies and drug interactions

3.3.1. CYP enzyme interactions

Preliminary investigation of the effect of a drug on CYP450 enzymes involves in vitro studies with human liver microsomes (HLMs), microsomes from recombinant CYP-expression systems, or hepatocytes. Estimates of the inhibitory constant (Ki) and the drug concentration reducing the activity of an enzyme by a half (IC_{50}) are obtained. The smaller the Ki value, the greater the binding affinity of the drug for the enzyme and the lower the drug concentration required to inhibit enzyme activity.

In vitro studies have reported cannabidiol inhibition of many CYP450 enzymes. A summary of Ki values from these in vitro studies performed in either HLMs or recombinant enzymes (R) is shown below (see Table 1) (Drugs used as the substrate are indicated where there are multiple listings for an enzyme).

Cannabidiol was observed to be a competitive inhibitor of CYP1 enzymes (CYP1A1, CYP1A2 and CYP1B1) and also produced potent mechanism-based inhibition of CYP1, particularly CYP1A1 [17]. Potent competitive inhibition of CYP2D6 with IC_{50} values ranging from 4.01 to 6.52 μM was observed for cannabidiol [19]. While differences were seen depending on the substrate and enzyme source used, cannabidiol was also observed to be a potent inhibitor of CYP2C9 and to be a direct inhibitor [20].

Cannabidiol was reported to be a competitive inhibitor of CYP3A enzymes, in particular CYP3A4 and CYP3A5 in an in vitro study using recombinant enzymes and HLMs. IC_{50} values reported for CYP3A4 and CYP3A5 were 11.7 μM and 1.65 μM, respectively, in recombinant enzymes and 9.18 μM in HLMs. Mixed inhibition was observed for CYP3A7 with an IC_{50} value of 24.7 μM [21] and for CYP2C19 [22].

An in vitro study investigated the inhibitory effect of several cannabinoids on CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4, and CYP1A2. An inhibitory effect by cannabidiol on CYP2B6 metabolism of the substrate drug bupropion was observed with a mean apparent IC_{50} value of 6.2 μM. Cannabidiol potently inhibited CYP2C19 metabolism of (S)-mephenytoin (IC_{50} value = 2.1 μM) and CYP2C9 metabolism of tolbutamide was also inhibited by cannabidiol (IC_{50} value = 2.5 μM) [23].

Using in vitro data, one approach to predict the likelihood of a drug–drug interaction is determining the ratio of the drug concentration at the active site of the enzyme [I]/Ki. [I] is the mean steady-state maximum plasma concentration (Cssmax) value of the inhibitor drug. If the ratio of [I]/Ki is <0.1, the likelihood of a drug interaction is remote, if it falls between 0.1 and 1 a drug interaction may be possible and if the ratio is >1 a drug interaction is likely.

Since the estimated Ki value is an integral part of this prediction, the accuracy of Ki must be considered. Nonspecific binding of cannabidiol, including binding to microsomal proteins and labware may occur with in vitro studies resulting in overestimating Ki and IC_{50} and underestimating the true interaction potential [24]. Recent in vitro studies with cannabinoids have used corrected values in models

Table 1. Ki values reported from in vitro studies using HLMs or R for different CYP450 enzymes.

Enzyme	Test system	Ki (μM)	Reference
CYP1	HLMs	1.75	[17]
CYP1A1	R	0.155	[17]
CYP1A2	R	2.69	[17]
CYP1B1	R	3.63	[17]
CYP2A6	R	55.0	[18]
CYP2B6	R	0.69	[18]
CYP2D6 (Dextromethorphan)	HLMs	2.42	[19]
CYP2D6 (Dextromethorphan)	R	2.69	[19]
CYP2D6 (AMMC)	R	1.16	[19]
CYP2C9 (Warfarin)	HLMs	3.46–5.60	[20]
CYP2C9 (Diclofenac)	HLMs	9.88	[20]
CYP2C9 (Warfarin)	R	0.954	[20]
CYP2C9 (Diclofenac)	R	2.31	[20]
CYP3A4/5	HLMs	6.14	[21]
CYP3A4	R	1.00	[21]
CYP3A5	R	0.195	[21]
CYP3A7	R	12.3	[21]
CYP2C19	R	0.793	[22]

AMMC = 3-[2-(N,N-Diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin; HLMs = human liver microsomes; Ki = inhibitory constant; R = recombinant enzymes.

Table 2. A summary of the mean values for $IC_{50,u}$ and $K_{i,u}$ (R,HLMs) and type of inhibition observed by Nasrin et al.

Enzyme	Mean $IC_{50,u}$ (μM)	Mean $K_{i,u}$	Type of inhibition
CYP1A2	0.13,0.67	0.12,0.21	M
CYP3A4	0.19,0.45	0.093,0.22	C
CYP2B6	0.13,0.26	0.068,0.22	C
CYP2C9	0.22,0.48	0.093,0.19	C
CYP2C19	0.16,0.36	0.050,0.092	C/M
CYP2D6	0.19,0.52	0.074,0.31	C
CYP2E1	0.037,0.14	0.021,0.058	C

C = competitive inhibition; M = mixed inhibition; HLMs = human liver microsomes; $IC_{50,u}$ = half maximal inhibitory concentration corrected for unbound fraction; $K_{i,u}$ = inhibitory constant corrected for unbound fraction; R = recombinant enzymes.

to extrapolate in vitro data into in vivo predictions of potential drug–drug interactions for cannabinoids.

A study by Nasrin et al. 2021 [25] calculated binding corrected $IC_{50,u}$ and $K_{i,u}$ values for cannabidiol using pooled adult HLMs. The mean values observed for the different CYP enzymes (which are considerably lower than those reported in Table 1) are summarized in Table 2.

Nasrin et al. 2021 [25] used basic mechanistic static modeling to predict the potential for in vivo drug–drug interactions. Modeling predicted a strong potential for pharmacokinetic interactions with cannabidiol (both oral and inhaled) with CYP1A2, CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. In the modeling, the authors used a Cmax of 703 nM for an oral dose of 800 mg and for 20 mg inhaled cannabidiol, the Cmax was 10.3 nM [25].

Bansal et al. conducted two in vitro human liver microsome studies to investigate the likelihood of cannabidiol and its metabolites precipitating pharmacokinetic drug–drug interactions by inhibition of CYP enzymes. Recognizing the potential for overestimating IC_{50} and Ki and underestimating inhibition potency, due to nonspecific binding, these studies calculated $IC_{50,u}$ values. The $IC_{50,u}$ values reported in the first study are shown in Table 3.

Various forms of mechanistic static models calculating AUCR (ratio of the area under the plasma probe drug concentration in the presence or absence of the inhibitor compound) were used in these studies. The initial study observed that cannabidiol reversibly inhibited CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A and was a time-dependent inhibitor (TDI) of CYP1A2, CYP2C19, and CYP3A with the mechanism for TDI unknown. Based on modeling, the initial study predicted strong drug interactions with CYP2C9, CYP2C19, and CYP3A and moderate drug interactions with CYP1A2 and CYP2D6. The authors acknowledged that these predictions were based on static Cmax concentrations after oral dosing, and that use of physiologically based pharmacokinetic modeling may lead to improved predictions of interactions [24].

The second study investigated the potential for drug–drug interactions of cannabidiol and its metabolites with CYP2A6, CYP2B6, and CYP2C8. The authors concluded that cannabidiol produced potent reversible inhibition of CYP2B6 and CYP2C8, while inhibition of CYP2A6 was weak and reversible. TDI of CYP2A6, CYP2B6 or CYP2C8 was not observed for cannabidiol or its metabolites. Observed predictions of the potential for drug–drug interactions varied depending on the models used. The outcomes from models ranged from modest to no pharmacokinetic interactions between cannabidiol (at oral doses greater than 700 mg) and drugs metabolized by CYP2B6 or CYP2C8 [26].

Many commonly prescribed drugs are metabolized by the CYP enzymes and may be candidates for drug–drug interactions with cannabidiol. For example, CYP3A4 is involved in the metabolism of about a quarter of all commonly used drugs and inhibition of CYP3A4 may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildafenil, antihistamines, haloperidol, antiretrovirals, and some statins. CYP2D6 metabolizes many antidepressants and inhibition has the potential to increase serum concentrations of selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, beta-blockers, and opioids such as codeine and oxycodone [27]. Some standard drug interaction checking platforms do not distinguish between minor and major CYP metabolic pathways and clinical significance data is not readily available for many potential cannabidiol interactions.

3.3.2. UGT enzyme interactions

The UGT family of enzymes catalyze glucuronic acid conjugation and are important in the metabolism of many small molecule drugs and endogenous compounds. Impaired glucuronidation of drugs via inhibition due to drug interactions may lead to slower elimination of drugs and accumulation of toxic metabolites. Limited data are available on the effect of cannabidiol on these enzymes. When studied in vitro using HLMs, cannabidiol was observed to inhibit ethanol glucuronidation, which is mainly catalyzed by UGT1A9 and UGT2B7. The Ki value reported was 3.1 mg/L [28].

A recent in vitro study investigated the inhibitory potential of cannabidiol using microsomes isolated from HEK293 cells which overexpressed individual recombinant UGTs and in microsomes from human liver and kidney specimen

Table 3. Mean $IC_{50,u}$ values reported for different CYP450 enzymes from in vitro studies using pooled HLMs.

Enzyme	Mean $IC_{50,u}$ (μM)
CYP1A2	0.45
CYP2C9	0.17
CYP2C19	0.30
CYP2D6	0.95
CYP3A	0.38

HLMs = human liver microsomes; $IC_{50,u}$ = half maximal inhibitory concentration corrected for unbound fraction.

microsomes. Strong inhibition of UGTs 1A6, 1A9, 2B4 and 2B7 by cannabidiol was observed while inhibition of UGT2B17 was reported to be marginal. Mean unbound IC_{50} values determined with different substrates and in vitro systems ranged from 0.14 to 1.4 μM for UGT1A6, 0.22 to 2.5 μM for UGT2B4, 0.82 to 22 μM for UGT2B7, and 0.073 to 1.5 μM for UGT1A9. The major metabolite of cannabidiol, 7-OH-CBD, did not exhibit any significant inhibition against the UGTs tested. The mean unbound IC_{50} values observed are in a range observed after oral administration of a 400 mg dose of cannabidiol (0.76 μM) making it plausible for drug–drug interaction via this pathway to occur [29].

UGT enzymes are involved in the glucuronidation of a range of drugs and inhibition of these enzymes reduces the excretion of substrate drugs. Since many commonly used medications undergo glucuronidation, cannabidiol should be used with caution in patients who are on medications that undergo glucuronidation and when commencing these medications. Patients should be carefully monitored for side effects [30].

3.3.3. Drug transporter interaction

The effect of cannabidiol on the efflux transporter P-gp has been studied in vitro using different cell lines and differing results have been observed. Cannabidiol did not inhibit P-gp with human T lymphoblastoid leukemia or in mouse fibroblast MDR1 transfected cell lines [31]. However, cannabidiol inhibited P-gp mediated transport in a study using Caco-2 and LLC-PK1/MDR cells. While the IC_{50} observed in this study (8.44 μM) was much higher than plasma cannabidiol concentrations commonly observed, the authors noted that sufficiently high concentrations may be achieved in the gastrointestinal tract when cannabidiol is administered orally to influence bioavailability [32]. A review on the safety and side effects of cannabidiol also noted that very high oral doses would be required to achieve plasma cannabidiol concentrations in the range of IC_{50} values reported in in vitro studies and suggested that the cannabidiol effect on transporters should be investigated in the concentration range of 0.03–0.06 μM [33].

The MRP1 transporter, which is implicated in phase II metabolism, was observed in vitro to be inhibited by cannabidiol [34]. Data submitted to the U.S. Food & Drug Administration (FDA) by the sponsor of cannabidiol oral solution (Epidiolex®) states that cannabidiol was not found to be an inhibitor of a range of other hepatic and renal drug transporters [35].

In vitro studies have shown that the inactive metabolite of cannabidiol, 7-carboxy-cannabidiol (7-COOH-CBD), is a substrate of P-gp and also an inhibitor of both BCRP, and the bile salt export pump (BSEP). Drugs that are substrates of these transporters may potentially be affected by this metabolite [30].

Further research is needed to confirm the clinical presence and relevance of transporter interactions. Until this research is undertaken, caution is recommended when cannabidiol is co-administered with drugs that are P-gp substrates, including narrow therapeutic index (NTI) drugs, such as digoxin and drugs that are BCRP and BSEP substrates.

3.3.4. Carboxylesterase inhibition

The esterase, carboxylesterase 1 (CES1), is expressed in the human liver and catalyzes the hydrolysis of a range of drugs and endogenous compounds. An in vitro study using the S9 fraction of human embryonic kidney 293 cells expressing CES1 observed potent inhibition of CES1 by cannabidiol. The mechanism of inhibition was reversible and observed to be a mixed competitive, noncompetitive inhibition with a mean Ki value of 0.974 μM [36]. In an in vitro study investigating the effect of cannabidiol on the two-step hydrolysis of heroin, cannabidiol was observed to be a potent in vitro inhibitor of hydrolysis. The IC_{50} values for the two steps of heroin hydrolysis were 14.7 and 12.1 μM, respectively. However, when the ratio of an estimated unbound cannabidiol Cmax to IC_{50} was calculated, the value was below the possible in-vivo drug–drug interaction FDA and European Medicines Agency cutoff value of 0.02. Based on this, the authors suggested that the observed in vitro inhibition was unlikely to be clinically relevant [37]. In a physiologically-based pharmacokinetic model, simultaneous administration of single-dose methylphenidate and cannabidiol (2.5–10 mg/kg) did not result in a significant interaction. In contrast, a mild interaction was reported to be likely with multiple cannabidiol doses (10 mg/kg twice daily) [38].

4. Preclinical (animal studies) and clinical observations

While there is a paucity of clinical trials in humans, there are extensive preclinical studies in animal models. The following section presents data obtained from studies in animal models and clinical observations. Where data are available from preclinical and clinical studies in each of the classes of drugs, the data will be compared and discussed. See Tables 4 and 5 for a brief reference summary of cannabidiol drug interactions based on human data.

4.1. Anticonvulsants

4.1.1. Animal studies

Cannabidiol is administered to patients with rare types of epilepsy who are also receiving other anticonvulsant medications. Using a mouse model of epilepsy, cannabidiol at a dose of 100 mg/kg was observed to enhance the effect and decrease the median effective dose (ED_{50}) of topiramate, oxcarbazepine, pregabalin, tiagabine, and gabapentin. The anticonvulsant effectiveness of lamotrigine or lacosamide was not changed and the anticonvulsant effect of levetiracetam was reduced [46]. Cannabidiol 100 mg/kg was associated with an increase in serum concentration with no change in brain concentration of topiramate and oxcarbazepine. Increases in gabapentin in both serum and brain were seen, while increased concentration in brain but not plasma of tiagabine and lacosamide were demonstrated. Concentrations of lamotrigine, pregabalin, and levetiracetam in brain and serum were unchanged. Topiramate increased brain and serum cannabidiol concentrations. Oxcarbazepine and pregabalin increased brain but not serum cannabidiol.

Table 4. Potential drug interactions between cannabidiol and antiseizure medication.

Drug	Study design	CBD dose	Drug dose	Other medications*	Potential for interactions with other medications	Reported outcomes	Clinical recommendations (therapeutic drug or clinical monitoring and dose adjustments)	References
Brivaracetam	Case series	5 mg/kg/day titrated to 20–50 mg/kg/day: CBD dose stable at least 2 weeks before BRV measurement	Dose: 50–300 mg. Dose unchanged during study in 4/5 patients	CLB, LAC, LAM, PGB, PHB, PER, VPA	Yes	Increased plasma brivaracetam concentrations.	TDM where available; clinical monitoring; dose adjustment may be required.	[39]
Clobazam**	Phase II double blind placebo controlled randomized trial	Epidiolex® (CBD 100 mg/mL) titrated to 20 mg/kg/day in two divided doses (maximum dose for 21 days)	10–20 mg (CBD group) and 5–20 mg daily (placebo group)	No more than two other ASM. CBZ, ESL, PHB, LAC, LAM, LEV, OCB, VPA, antihistamines, antianaemic drugs and folic acid.	Yes	Increased active metabolite nCLB concentrations (days 1 to 33). Reported adverse events (not broken down by drug) included diarrhea (n = 6), nausea (n = 3), vomiting (n = 3), dizziness (n = 2), sedation (n = 2), somnolence (n = 2), and dermatitis (n = 2). A patient withdrew due to a seizure cluster.	TDM of CLB and nCLB concentration (where available), along with clinical monitoring. Dose adjustment may be required.	[40]
	Expanded access trial	5 mg/kg/day increased to 20 mg/kg/day (over 4 weeks) and to 25 mg/kg/day (week 8)	Baseline mean dose 1 mg/kg/day (range 0.18–2.24 mg/kg/day)	FEL, LAC, LAM, LEV, PTN, RUF, VIG, VPA, ZON.	Yes	At week 8, 2–6 fold increase in nCLB concentration. Adverse events included restless sleep, urinary retention, tremor, loss of appetite, ataxia, irritability, and drowsiness. Adverse events resolved with CLB dose adjustments.		[41]
	Open-label trial	Epidiolex® (CBD 100 mg/mL) 5 mg/kg/day, increasing every 2 weeks by 5 mg/kg/day to a maximum of 50 mg/kg/day		CBZ, CLO, ESL, ETH, EZO, LAC, LAM, LEV, OCB, PER, PGB, PHB, PTN, RUF, TOP, VIG, VPA, ZON.	Yes	Increased nCLB concentrations with increasing CBD dose in pediatric and adult patients. Sedation with increased nCLB in adult patients.		[42]
	Open-label trial	Epidiolex® (CBD 100 mg/mL) 750 mg twice daily (for 75 kg adult = 20 mg/kg/day). With either no titration or 10 day titration	5 mg twice daily (victim drug: 5 mg in the morning day 1 and final day with 7–14 days concomitant dosing with CBD; perpetrator drug: 5 mg twice daily with 21 days of concomitant CBD dosing and 5 mg in the morning on the final day)			Increased n-CLB, and active metabolite 7-OH-CBD. Adverse events resulting in study withdrawal included severe rashes (n = 2).		[43]
Eslicarbazepine rufinamide topiramate zonisamide	Open-label trial	Epidiolex® (CBD 100 mg/mL) 5 mg/kg/day, increasing every 2 weeks by 5 mg/kg/day to a maximum of 50 mg/kg/day		CBZ, CLB, CLO, ESL, ETH, EZO, LAC, LAM, LEV, OCB, PER, PGB, PHB, PTN, RUF, TOP, VIG, VPA, ZON.	Yes	Increased TOP, RUF concentrations (pediatric and adult patients) and ZON, ESL (adult patients) within normal therapeutic ranges.	Clinical monitoring is recommended.	[42]
Stiripentol	Open-label, fixed sequence (bi-directional interaction study)	750 mg twice daily	750 mg twice daily			28–55% increase in plasma stiripentol exposure. No important effect on CBD exposure, minor decrease in 7-OH-CBD (29%) and 7-COOH-CBD exposure (13%). Adverse effects: rash, 'feeling drunk,' and menstrual discomfort.	Clinical monitoring recommended. Dose adjustments may be required.	[43]
	Phase II randomized trial	Epidiolex® (CBD 100 mg/mL) 20 mg/kg/day (10 day dose titration)	625 (500–2000) mg/day	CLB, ETH, LAC, LAM, TOP, VPA.	Yes	A small increase in stiripentol concentration. Adverse events included rash (n = 1) and elevated LFTs (n = 2).		[44]

(*Continued*)

Table 4. (Continued).

Drug	Study design	CBD dose	Drug dose	Other medications*	Potential for interactions with other medications	Reported outcomes	Clinical recommendations (therapeutic drug or clinical monitoring and dose adjustments)	References
Valproate	Systematic chart review	Epidiolex® (CBD 100 mg/mL) highest CBD dose 13.6 ± 5.0 mg/kg/day	VPA 26.2 ± 15.4 mg/kg/day	Antiseizure medications, including CLB (individual cases not described).	Yes	Thrombocytopenia – independent of VPA dose and concentration. Results were not-statistically significant.	Clinical and laboratory test monitoring is recommended. Liver function tests are recommended at baseline, 1, 3, 6 months and when clinically indicated. Platelet monitoring is recommended. Dose adjustments may be required.	[45]
	Open-label trial	750 mg twice daily. A mix of no titration, 3, and 10 day titration	VPA 500 mg twice daily (victim drug: 300 mg in the morning, titrated over 5 days to 500 mg twice daily; perpetrator drug: no titration)			Rash was reported before protocol change to incorporate dose titration. CBD unlikely to have a clinically significant effect on the pharmacokinetics of total VPA concentration (free valproate not measured).		[43]
	Open-label trial	Epidiolex® (CBD 100 mg/mL) 5 mg/kg/day, increasing every 2 weeks by 5 mg/kg/day to a maximum of 50 mg/kg/day		CBZ, CLB, CLO, ESL, ETH, EZO, LAC, LAM, LEV, OCB, PER, PGB, PHB, PTN, RUF, TOP, VIG, VPA, ZON.	Yes	Increased mean AST and ALT within normal range. Elevated LFTs lead to discontinuation in some cases.		[42]
	Phase II randomized trial and in vitro study	Epidiolex® (CBD 100 mg/mL) target dose 20 mg/kg/day (10 day dose titration)	VPA 1115 mg (200–2500 mg) daily	No more than two other drugs, including CBZ, CLB, CLO, LAC, LAM, LEV, LOR, OCB, RUF, ZON.	Yes	Withdrawal due to diarrhea and nausea and elevated liver function. Altered LFTs have also been reported in several phase III clinical trials.** **In vitro study**: No alteration with CBD or 7-COOH-CBD on valproate plasma protein binding.		[44]

* May include different combinations for each patient.
** A comprehensive overview of Phase III trials is not included in this table as they are covered in a separate publication.
ALT = alanine aminotransferase; ASM = antiseizure medication; AST = aspartate aminotransferase; BRV = brivaracetam; CBD = cannabidiol; CBZ = carbamazepine; CLB = clobazam; CLO = clonazepam; 7-COOH-CBD = 7-carboxy-cannabidiol; ESL = eslicarbazepine; ETH = ethosuximide; EZO = ezogabine; FEL = felbamate; LAC = lacosamide; LAM = lamotrigine; LEV = levetiracetam; LFT = liver function test; LOR = lorazepam; nCLB = N-desmethylclobazam; OCB = oxcarbazepine; 7-OH-CBD = 7-hydroxy-cannabidiol; PER = perampanel; PGB = pregabalin; PHB = phenobarbital; PTN = phenytoin; RUF = rufinamide; TDM = therapeutic drug monitoring; TOP = topiramate; VIG = vigabatrin; VPA = valproate or valproic acid; ZON = zonisamide.

Table 5. Potential drug interactions with cannabidiol.

Drug	Study design	CBD dose	Drug dose	Reported outcomes	Clinical management (therapeutic drug or clinical monitoring and dose adjustments)	Reference
Citalopram or escitalopram	Open-label trial	Initiated 200 mg/day and titrated to 600–800 mg/day		Elevated citalopram concentration.	TDM (where available) and clinical monitoring. Dose adjustments may be required.	[52]
Fluoxetine	Case report	18 mg twice daily (CBD 200 mg/mL, other cannabinoids up to 4 mg/mL, including THC no more than 0.4 mg/mL)	Fluoxetine 20 mg/day	Insomnia, hyperactivity, increased agitation, exacerbation of obsessive-compulsive disorder. Possible to probable drug interaction based on the Naranjo Drug Interaction Probability Scale.	Possible drug-gene-drug interaction. In CYP2D6 poor metabolizers (where pharmacogenetic testing results are available), monitoring of fluoxetine concentrations is recommended (where available) and dose adjustments may be required. Clinical monitoring is recommended for all patients.	[53]
Everolimus and sirolimus	Case report	Titrated to 200 mg daily (9.3 mg/kg/day) and then 500 mg daily (20.4 mg/kg/day)	Everolimus 0.15 mg/kg/day, increased to 0.6 mg/kg/day and then reduced to 0.3 mg/kg/day	Increased and variable everolimus concentrations.	TDM (where available), laboratory, and clinical monitoring. Dose adjustments may be required.	[70]
	Retrospective review	5–20 mg/kg/day		Increased everolimus and sirolimus concentrations. Adverse events were noted for some patients.		[71]
Lithium	Case report	5 mg/kg/day and titrated to 10 mg/kg/day, soon after which clinical manifestations of lithium toxicity became apparent	Lithium 600 mg in the morning, 300 mg in the afternoon, and 600 mg at bedtime.	Elevated lithium concentration. Hypersomnolence, ataxia, and decreased oral intake.	Clinical and lithium concentration monitoring (where available) is recommended. Dose adjustments may be required.	[61]
Methadone	Case report	CBD oil (25 mg/mL) 5 mL three times daily and then (50 mg/mL) six times daily.	7.5 mg twice daily.	Raised methadone concentration. Sleepiness and fatigue.	Clinical monitoring is recommended. Dose adjustments may be required.	[56]
Tacrolimus	Case reports and/or series	**Case report** Titrated to 20 mg/kg/day and then up to 25 mg/kg/day	5 mg twice daily with subsequent held doses and dose reductions required.	Altered tacrolimus concentrations.	Clinical and tacrolimus concentration monitoring (where available) is recommended. Dose adjustments may be required.	[72]
		Case series CBD 50–150 mg twice daily. Dose reduction was required for a patient that experienced nausea.	Dose reduction was required (n = 2) due to elevated tacrolimus concentration. Notably, pruritis preceded CBD initiation in one case. In another patient, tacrolimus concentration decreased, however this resolved a week later.			[73]
Tamoxifen	Case report	Product contained 20 mg/mL CBD and 2 mg/mL THC. Dose of 40 mg/day CBD and 4 mg/day THC	20 mg daily	Decreased tamoxifen active metabolite concentration. Naranjo adverse drug reaction probability scale score = 6 (probable).	Caution recommended in CYP2D6 and CYP3A4 poor metabolizers (where pharmacogenetic testing results are available).	[68]

(*Continued*)

Table 5. (Continued).

Drug	Study design	CBD dose	Drug dose	Reported outcomes	Clinical management (therapeutic drug or clinical monitoring and dose adjustments)	Reference
Warfarin	Case reports	Epidiolex® (CBD 100 mg/mL) 5 mg/kg/day in two divided doses, titrated in 5 mg/kg/day increments weekly to a maximum dose of 40 mg/kg/day	Initially 7.5 mg/day. Warfarin dose reduced by 30%.	Elevated INR.	Potential dose threshold. Monitor INR and adjust dose accordingly.	[63]
		Epidiolex® (CBD 100 mg/mL) 5 mg/kg/day in two divided doses, titrated by 5 mg/kg/day weekly to 20 mg/kg/day (patient weight 116.1 kg)	80 mg weekly. Warfarin dose reduced by 20% to 65 mg weekly.	Elevated INR. Drug Interaction Probability Scale = 4 (Possible interaction).		[64]
		Oromucosal CBD 5.3 mg and THC 0.3 mg daily and 0.625 mg CBD and 0.625 mg THC when required	Stable dose 22.5 mg weekly	Case report involving low dose CBD with no interaction. Potential dose threshold.		[66]

CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol; INR = international normalized ratio; TDM = therapeutic drug monitoring.

These data suggest the interactions are in part a result of pharmacokinetic interactions. However, these results should be interpreted with caution as a single concentration rather than an AUC was reported, and not all the changes in antiseizure medication (ASM) efficacy are explained [46].

In mice given cannabidiol 12 mg/kg to give a plasma concentration of 411 ± 87 ng/mL and co-administered clobazam, significant interactions are seen. Plasma clobazam AUC increased sixfold and brain exposure to clobazam was similarly increased. AUC of N-desmethylclobazam (nCLB) was increased, and time to maximum plasma concentration (Tmax) delayed [47]. This study also demonstrated that clobazam and cannabidiol, positive allosteric modulators of the $GABA_A$ receptor, augmented GABA mediated current but were not synergistic in this [47].

In rats administered cannabidiol, single-dose cannabidiol was associated with increased carbamazepine AUC and decreased AUC of the metabolite carbamazepine-10,11-epoxide. In contrast, repeated cannabidiol administration daily for 2 weeks resulted in a reduced AUC. While the single cannabidiol dose effect likely occurs through CYP3A inhibition, the mechanism of interaction in the prolonged cannabidiol dosing is unclear [48].

4.1.2. Clinical studies

Cannabidiol may be used in combination with other ASM in either treating some forms of epilepsy or where ASM are being used as mood stabilizers or to treat neuropathic pain.

In an open-label safety study of patients with treatment-resistant epilepsy, following cannabidiol administration in combination with clobazam, increased active metabolite nCLB concentrations were observed [42]. Similar observations were reported in a phase II trial [40]. The interaction is thought to be due to CYP2C19 inhibition [41]. Gaston et al. 2017 [42] also reported that with higher nCLB concentrations, there were more frequent reports of sedation in adult participants [42]. In the setting of Dravet Syndrome and Lennox Gastaut Syndrome, cannabidiol has been reported to have antiseizure activity independent of other ASM. Pharmacokinetic and pharmacodynamic interactions between cannabidiol and clobazam may result in increased antiseizure effect and potential adverse effects [49].

In the aforementioned study by Gaston et al. 2017 [42], elevated rufinamide, topiramate and zonisamide concentrations, within normal therapeutic ranges, were reported. A dose dependent increase in zonisamide concentration was observed in adults but not pediatric study participants [42].

In healthy volunteers, cannabidiol had a very modest impact on clobazam AUC and Cmax and a greater impact on nCLB AUC and Cmax. Stiripentol AUC was increased slightly with cannabidiol co-administration. Cannabidiol had no effect on these pharmacokinetic parameters of valproate. Valproate had no impact on cannabidiol or 7-OH-CBD metabolite kinetics, although a slight increase in 7-COOH-CBD was noted. Clobazam increased and stiripentol decreased AUC and Cmax of some metabolites of cannabidiol but had no impact on cannabidiol [43]. Elevated liver transaminases have been reported in open-label and randomized trials and thrombocytopenia in a pediatric chart review with the combination of cannabidiol and valproate [42,44,45,50].

There is case series data of increased plasma brivaracetam concentrations occurring during co-administration with cannabidiol [39].

Clinical and therapeutic drug monitoring should be implemented, where possible, with concurrent ASM and cannabidiol use.

4.2. Antidepressants

4.2.1. Animal studies

In a mouse model of depression, doses of cannabidiol (7 mg/kg), fluoxetine (7 mg/kg), and desipramine (2.5 mg/kg) had no antidepressant effect when given alone. With a dose increase of each individual agent to cannabidiol 10 mg/kg, fluoxetine 10 mg/kg or desipramine 5 mg/kg, an antidepressant effect was seen. When given together, a significant effect was seen with the combination of fluoxetine 7 mg/kg and cannabidiol 7 mg/kg, but not desipramine 2.5 mg/kg and cannabidiol 7 mg/kg. The effect of cannabidiol alone at 10 mg/kg was blocked by inhibition of serotonin synthesis, indicating cannabidiol's antidepressant effect is mediated through serotoninergic mechanisms [51]. In vitro studies suggest fluoxetine metabolism is impacted weakly by cannabidiol [52]. Taken together, these data indicate that the antidepressant effect of combined subtherapeutic doses of cannabidiol and fluoxetine is pharmacodynamic rather than pharmacokinetic in nature. In contrast, metabolism of citalopram and escitalopram is inhibited by cannabidiol [52].

4.2.2. Human studies

A recent case report in a patient with a homozygous CYP2D6*4 genotype conferring null activity highlighted the potential impact of drug–gene interactions with cannabidiol (18 mg twice daily) and fluoxetine [53].

In an open-label trial, a modest increase in a single steady state concentration of citalopram was observed at week 8 compared to baseline with the combination of citalopram or escitalopram with cannabidiol. The interaction was attributed to cannabidiol inhibition of CYP3A4 and CYP2C19 [52].

4.3. Opioids

4.3.1. Animal studies

In mice, an antinociceptive effect of morphine 0.32–10 mg/kg or cannabidiol 10–40 mg/kg was demonstrated in the acetic acid-stimulated stretching model of pain. The combination of cannabidiol and morphine had a synergistic effect in this model. However, in the other two anti-nociceptive models tested (acetic acid-decreased operant responding for palatable food and hot-plate thermal nociception), cannabidiol reduced morphine responses. These complex responses suggest the interaction is pharmacodynamic rather than pharmacokinetic [54].

Heroin is metabolized by two hydrolytic steps, first to 6-Mono-acetyl morphine (6-MAM) and then to morphine. In vitro, the hydrolysis of heroin and 6-MAM is inhibited by

cannabidiol, with IC_{50} values of 14.7 and 12.1 μM, respectively. This was associated with increased behavioral responses elicited by these drugs [37]. In a rodent model where mice were pre-treated with cannabidiol at doses up to 120 mg/kg, no alteration in brain or blood concentrations of morphine, methadone or methylenedioxyphenyl-methamphetamine was seen with cannabidiol pre-treatment [55]. This is in contrast to the report described below, and reinforces the need for caution when extrapolating animal data to humans.

4.3.2. Human studies

In a pediatric case report involving concomitant methadone and cannabidiol, elevated methadone concentrations, somnolence, and fatigue were observed [56]. As a number of CYP450 enzymes are postulated to contribute to methadone metabolism, cannabidiol inhibition of CYP2B6, CYP3A4, CYP2C19, and to a lesser extent CYP2C9 may be involved [57,58]. A pharmacodynamic interaction may also contribute as somnolence and fatigue are common adverse effects associated with cannabidiol [11].

In healthy volunteers receiving either placebo, a single dose of 400 mg cannabidiol or 800 mg cannabidiol and then IV fentanyl (0.5 μg/kg and 1.0 μg/kg), no increase in adverse events or change in physiological parameters was seen with cannabidiol. AUC of cannabidiol was not affected by fentanyl. No plasma fentanyl was detected in any subject [59]. In a recent systematic review, no opioid sparing effects of cannabidiol were identified in higher quality studies [60].

4.4. Psychotropic drugs

4.4.1. Animal studies

Pre-treating mice with cannabidiol at doses up to 120 mg/kg resulted in increased brain and blood concentrations of tetrahydrocannabinol, cocaine, and phencyclidine [55].

4.4.2. Human studies

In a case report involving cannabidiol and lithium, an elevated lithium concentration and symptoms consistent with lithium toxicity were observed [61]. The AUC and half-life of caffeine are increased in healthy volunteers administered cannabidiol 750 mg twice daily to a steady state [62].

4.5. Other drug classes

4.5.1. Anticoagulant and antiplatelet agents

In patients taking warfarin and purified cannabidiol or products likely containing cannabidiol and tetrahydrocannabinol, there have been case reports of increased international normalized ratio (INR) and a clinically significant drug interaction via CYP2C9 inhibition is predicted [63–65]. The notion of a dose threshold for drug interactions was highlighted in a recent case report, where there was minimal impact on INR with concomitant warfarin and oromucosal medicinal cannabis. The authors suggested that the serum concentration of cannabinoids was less than what would be required to exert an inhibitory effect on CYP enzymes [66]. There is a theoretical risk of increased bleeding when antiplatelet and anticoagulant drugs are combined with cannabidiol, based on cannabidiol inhibition of platelet aggregation in vitro [67].

4.5.2. Anti-cancer drugs

Patients with cancer are a population where it is likely to see use of cannabinoids in combination with anti-cancer treatments. Few reports are available on whether drug interactions occur when cannabidiol is combined with different chemotherapy agents. One case report investigated the use of oral formulation of cannabidiol (also containing a small percentage of tetrahydrocannabinol) at a dosing of 40 mg/day in patient taking tamoxifen which undergoes metabolism by CYP3A4 and CYP2D6 to the active metabolite endoxifen. When tamoxifen and metabolite concentrations were measured, the results suggested probable inhibition of enzymes by cannabidiol and highlighted the need to fully investigate this possible interaction [68].

4.5.3. Anti-fungal drugs

The effect of CYP3A4 inhibition on cannabidiol kinetics was investigated in rats administered ketoconazole. The AUC for lower dose cannabidiol was increased by ketoconazole, but not the AUC for higher dose suggesting saturable metabolism. In this study, cannabidiol at higher doses of 10 and 50 mg/kg but not 1 mg/kg inhibited CYP3A4 demonstrated with the erythromycin breath test. Cmax corresponding to the 1, 10 and 50 mg/kg cannabidiol doses were 0.12 μM, 1.23 μM and 11.4 μM, respectively [69].

4.5.4. Immunosuppressant drugs

Elevated and variable everolimus concentrations were reported with combined use with cannabidiol in a pediatric case report, possibly via a CYP3A4 interaction [70]. In a retrospective review, in 19 of 25 patients taking cannabidiol, elevated mTOR inhibitor (everolimus or sirolimus) concentrations were reported. Confounding effects of drug interactions with coadministered drugs cannot be excluded [71]. There have been case reports and/or series where altered tacrolimus concentrations have been observed with concurrent use of cannabidiol only or predominant products [72,73]. However, there are also case reports with tetrahydrocannabinol containing and predominant products [74,75]. Although the interaction has been proposed to occur via CYP3A and/or P-gp [75], it is uncertain how much of a role intra-individual variability plays in these published cases. Nonetheless, concentration monitoring and dose adjustments (as required) are recommended. Cannabidiol may also exert independent effects on the immune system.

5. Discussion

There has been a surge in public interest and research into using cannabidiol as a medicine. Cannabidiol is one of the two major phytocannabinoids in cannabis. Its pharmacodynamic profile at both cannabinoid and non-cannabinoid receptors is different to that of the other major cannabinoid, tetrahydrocannabinol, although they are both lipids and require metabolism for excretion [76]. Cannabidiol has been used to treat many different clinical conditions, including rare types of epilepsy, managing pain, anxiety, and sleep disorders [77]. Since cannabidiol is commonly added to

existing drug regimens, interactions between cannabidiol and other co-administered drugs may occur. The extent of interaction between drugs depends on the plasma drug concentrations of each drug and the systemic exposure measured by the AUC. Plasma drug concentrations and AUC are determined by the dose, dosing regimen, formulation, route of administration, and drug pharmacokinetics. Additional variability may be conferred by pharmacogenomic diversity.

Daily cannabidiol doses vary from a few milligrams to grams per day, depending on the clinical indication. A systematic review of clinical studies reported dosing ranging from <1 mg/kg/day to 50 mg/kg/day [78]. Some clinical studies observed biphasic and inverted U-shaped dose–response curves, influencing the dose administered [79,80]. With such an extensive range of dosing, stratifying dosing into low, medium or high dosing may assist in assessing the potential for drug–drug interactions. A recent review of cannabidiol classified a low dose as ≤1 mg/kg/day; a medium dose was 1–10 mg/kg/day, and a high dose was 10–50 mg/kg/day [81]. A similar dose stratification has been described in the literature [24].

In some countries, cannabidiol is available to consumers as over the counter products (OTC) or food supplements, and the actual amount of cannabidiol ingested by a consumer is difficult to ascertain. Studies analyzing the contents of a range of OTC cannabidiol products sold online or available in the United States of America and Europe reported the actual content of cannabidiol might differ substantially from the content stated on the product label, in which other cannabinoids, including tetrahydrocannabinol, other pharmacologically active substances and contaminants such as pesticides and heavy metals may also be present [82,83]. Contaminants and other substances may influence the pharmacological effects, side effects, toxicity, and drug interactions [84].

Predicting pharmacokinetic drug interactions is relatively straightforward, but quantifying the extent and clinical relevance can be complicated. Adding to this is the lack of certainty around dose and response, as receptor response is different at different concentrations, e.g. inverse agonist at low dose then antagonist at higher doses. It also affects other G-protein-coupled receptors at different concentrations [85]. This complex and evolving pharmacology makes pharmacodynamic interactions likely but difficult to predict.

Clinical and therapeutic drug monitoring (where possible) is encouraged, particularly with NTI drugs. Due to the potential for drug interactions with OTC and prescribed cannabidiol, screening questions to ascertain use need to be integrated as part of standard patient care. Comprehensive models of specialty pharmacist and clinical pharmacologist involvement in the care of patients taking cannabidiol can prospectively identify and manage potential drug interactions, through clinician prescribing guidance, patient counseling, dose adjustments, deprescribing and therapeutic drug monitoring [86–88].

Data on clinically relevant drug interactions with cannabidiol are scarce and data usually collected during preclinical, and phase I to III studies are missing for many cannabidiol medicines. Frameworks specific to cannabinoids and standard regulatory guidance for drug interaction studies are available [89,90]. With so many different cannabidiol products and differences in regulation of products, few real-world pharmacovigilance data are available to provide further guidance. Further, it highlights the importance of establishing well-designed pharmacovigilance strategies to obtain real-world data to inform clinicians and consumers and to guide the development of formal clinical studies [91].

6. Conclusion

Prediction of cannabidiol pharmacokinetic drug interactions and interim clinical guidance is currently based on existing data and basic principles. Although existing cannabidiol drug interaction data, including dose ranges, provide clues for further research, there are inherent flaws in the extrapolations of this data. There is a great need for high-quality research into cannabinoid drug interactions to facilitate a greater understanding of clinically relevant cannabidiol drug interactions. As further research emerges, it may become apparent that there is a dose range at which clinically relevant cannabidiol drug interactions are likely to occur.

7. Expert opinion

The widespread availability and use of non-prescribed and prescribed cannabidiol increase the likelihood that it may be taken with other medications. Available data on cannabidiol drug interactions is sparse and further high-quality research is needed. Health professional awareness of potential drug interactions with cannabidiol is critical for patient safety. Many of the drug interactions highlighted in this review, necessitate increased clinical, laboratory and/or therapeutic drug monitoring. In this article, published evidence related to drug interactions and dose ranges is explored to better understand clinical relevance and how this research may be translated into real-world clinical practice settings. Dose adjustments are likely to be necessary with many of the reported interactions. The review of drug interactions in this article has informed a suite of state-wide cannabis medicine prescribing guidance documents. The prescribing guidance documents have been adopted more broadly and are recommended by the Therapeutic Goods Administration (National Australian medicine regulator) as an educational resource for health professionals.

High-quality drug interaction studies are required to determine whether there is a dose threshold with cannabis medicine drug interactions. There are indicators that dose is important in the prediction of potential drug interactions with cannabidiol and this has important implications as lower doses of cannabidiol are readily available over the counter in many jurisdictions. The limitations of current published evidence are acknowledged, as are any extrapolations made from them. Rigorous drug interaction studies exploring the dose relationship in cannabidiol drug interactions are needed to move knowledge in this area forward.

Over time, a wider range of cannabidiol drug interactions and the doses at which they occur will become known. There is potential to improve patient safety outcomes by

undertaking this research. As health professionals, ongoing pharmacovigilance is important and therefore advising a definitive end-point would be counterintuitive to best practice. The review provides interim clinical guidance and highlights areas where research is required to further develop our understanding of clinically relevant cannabidiol drug interactions.

In the cannabis medicine research landscape, there are a plethora of evidence gaps. As health professionals are navigating best practices with a molecule that has not undergone typical drug research processes, researchers are retrofitting evidence as it becomes available. Due to a large number of evidence voids in the study of cannabis medicines, there is a multitude of promising areas in the field, including drug interactions requiring progression.

The extent of clinical guidelines that can be provided to health professionals is determined by the quantity and quality of published data available. Knowledge in this area is likely to build over time, and this will influence clinical guidance and translation into clinical practice settings in the next 5 to 10 years. Knowledge gains and real-world translation into clinical practice have the potential of improving patient safety outcomes.

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Declaration of interest

J Martin has a family member who is a shareholder in a cannabis start-up company in Australia. This has been fully declared to the funding agency and is subject to a governance order from the University of Newcastle regarding management of this potential conflict. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Author contributions

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