Review

Potential Drug Interactions with Cannabinoids in Selected Chronic Diseases: Epilepsy, Autism Spectrum Disorders, Oncology, Multiple Sclerosis and Pain

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Review

Potential Drug Interactions with Cannabinoids in Selected Chronic Diseases: Epilepsy, Autism Spectrum Disorders, Oncology, Multiple Sclerosis and Pain

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Abstract: The clinical practice implies a research translation that helps the use of scientific data and therapeutic evidence for patient benefits. This review critically summarizes the potential impact of cannabinoids in concomitance with other drugs in the following chronic diseases as Epilepsy, Autism Spectrum Disorders (ASD), Oncology, Multiple Sclerosis, and Chronic Pain. The potential interactions can change the predicted clinical outcomes of therapeutic protocols and need to be evaluated. Some of the effects would be additive, synergistic or antagonistic, but can also enroll changes in absorption, distribution, metabolism, particularly via cytochrome P450 (CYP) isoenzymes (e.g CYP2C9 and CYP3A4) and excretion. For instance, the combination of cannabis-derived compounds and the antifungal drug ketoconazole, a CYP3A4 inhibitor, increases plasma concentration of Δ-9-tetrahydrocannabinol (THC) and CBD (CBD). Opposable, rifampicin, a CYP3A4 inducer, stands out for the approximately 20-40% reduction in plasma THC levels and 50% to 60% for CBD. Other CYP3A4 inhibitors and inducers are likely to have a similar effect on plasma concentrations if co-administered. Indeed, pharmacokinetic interactions have been also reported with antiseizure drugs. Moreover, pharmacodynamic interactions between cannabinoids and drugs with sympathomimetic effects (eg tachycardia, hypertension), central nervous system depressants (eg drowsiness, ataxia), and anticholinergics (eg tachycardia and drowsiness) are also expected. Even though pending further studies, there is currently clinical evidence supporting drug interaction with cannabinoids, demanding doctors to evaluate the risk of drug combinations with cannabinoids. The tables herein provided were designed to facilitate the identification of biorelevant interactions that may compromise therapeutic efficacy and toxicity.

Keywords: Cannabinoids; Tetrahydrocannabinol; CBD; Drug-drug Interactions; F.I.R.E.S.; Cytochrome P450; Epilepsy; Cancer; Autism Spectrum Disorder

1. Introduction

In last years, several cannabinoid-based drugs have appeared, essentially for chronic pathologies. Their use in combination with other prescribed therapies can generate various types of pharmacological interactions, what is a common situation. The main objective of the present work is to alert the reader for the clinically relevant interactions between cannabinoids and other

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drugs that can impair the effectiveness and/or safety of the therapy, with the hope of promoting the maximum benefit and better quality of life of the patients, with the minimum associated risk.

The most commonly prescribed analgesic, psychotropic, and cardiovascular medications have proved potential adverse drug interactions, including with cannabinoids. Current data supports cannabinoid use only for a limited number of conditions as chemotherapy-induced nausea and vomiting, specific pain and spasticity syndromes, and certain forms of childhood epilepsy. Thus, physicians prescribing cannabinoids need to weigh the potential harms *vs.* perceived benefits carefully [1].

Recently (2023) it has developed a free web-based platform to screen for potential drug-drug interactions, the CANNabinoid Drug Interaction Review (CANN-DIR™), which is also a good tool to predict these potential events. The Summary of Product Characteristics (SmPC) of the approved drugs were used as a source of drug-drug interaction information, for medications sharing similar metabolic enzymes. This platform has the possibility to navigate and print results in any of the following ten languages: Chinese, English, French, German, Nepali, Polish, Russian, Spanish, Swedish, and Vietnamese [2]

In general, cannabinoids, such as Δ-9-tetrahydrocannabinol (THC) and CBD (CBD), can interact with other medications through various mechanisms. They can alter the pharmacokinetics of other drugs, particularly through interactions with the cytochrome P450 (CYP450) enzyme system, leading to increased or decreased levels of the drug in the bloodstream. Additionally, they can enhance or reduce the effects of other drugs, such as antiseizures and pain medications. It is critical to consult a healthcare professional before using cannabinoids in conjunction with other medications to avoid potential negative events [3]. These compounds, isolated previously from Cannabis plant, interact with the human endocannabinoid system. When taken in combination with other medications, they can produce a range of effects, beneficial and adverse. Briefly, the most notable interactions include:

1. Enhanced or reduced drug efficacy: Cannabinoids can affect the metabolism of other drugs and alter their effectiveness. For example, THC can increase the effects of blood-thinning drugs, leading to an increased risk of bleeding;
2. Interactions with hepatic metabolism: Many medications are processed through the liver, and cannabinoids can increase the rate at which they are metabolized, leading to reduced efficacy;
3. Adverse side effects: The combination of cannabinoids with certain drugs can lead to an increased risk of side effects, such as dizziness, fatigue, or nausea.
4. Increased sedation: Some drugs, such as opioids, can cause increased drowsiness when taken with cannabinoids, affecting individual ability to perform tasks such as driving or operating heavy machinery.

In an overall approach, drug interactions correspond to a change, which is quantifiable in the magnitude or duration of effects related to the simultaneous or previous administration of other drugs, foods, or the pathophysiological conditions of the patient. Generally, drug interactions due to pharmacodynamic mechanisms are less common, and those reported in the literature are explained by a pharmacokinetic pathway mediated by CYP450 enzymes, P-glycoprotein (P-gp), or by other drug transporters. For cannabinoids data indicated that:

- THC competitively inhibits CYP1A2, CYP2B6, CYP2C9 and CYP2D6 enzymes;
- CBD competitively inhibits CYP3A4, CYP2B6, CYP2C9, CYP2D6 and CYP2E1 enzymes;
- Cannabinol (CBN) competitively inhibits CYP2B6, CYP2C9 and CYP2E1 enzymes [4–6] ;

Absorption, distribution and elimination are important phenomena that determine drug disposition on the human body but that easily may suffer changes. For example, rate and extent of absorption can be affected by induction or inhibition of transporter proteins in the gut, chelation phenomena, changes in gastric pH or changes in gastrointestinal motility. The association of various food products by users, or even the usual consumption of fruit and vegetable juices, protein concentrates and/or lipids, as well as dietary supplements that include, in addition to proteins, vitamins and minerals, also medicinal plants (vegetable drugs/medicinal plants), which can lead to interactions [7] beyond those that we delve into in more detail here.

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In patients with epilepsy who are on a ketogenic diet, several previous aspects must be evaluated, namely the absorption and distribution conditions of the different drugs involved in the therapeutic protocols, as well as the best time for their administration in view of the internal environment in which they will be taken (fasting, before or after meals, in relation to the lipid and/or protein content of the plan, more acidic or more alkaline pH, etc.).

Before starting with the more specific information, it is important to point out that all the cannabinoids interact with CYP2C19, and their main metabolic pathways include the CYP2C9 and CYP3A4 isoenzymes. Although for the latter, polymorphisms may, in most individuals, not be problematic, the same is not linear regarding the CYP2C9 isoenzyme. This is due to the possible existence of polymorphisms or even silenced alleles that can lead, for example, to therapeutic failures and interactions with other drugs [8].

When the therapy is made with the vegetal drug, for instance the standardized Cannabis flower, used as a plant drug, it contains, in addition to cannabinoids, other types of compounds such as terpenes and flavonoids. Therefore, it should be noted that most of these structures are also CYP3A4 inhibitors. Flavonoids from other plant matrices such as diosmin and hesperidin (both venotropics), or those found in extracts from *Ruscus aculeatus* L., also venotropic, as well as from *Serenoa repens* (used in the treatment of benign prostatic hyperplasia) generate similar interactions at the level of that isoenzyme. Among the foods, grapefruit juice (often referred to in the medicines leaflets) contains furanocoumarins, as well as extracts of other fruits and/or vegetable drugs, which, by inhibiting this isoenzyme, compromise also the treatment [7].

In combination with cannabis-derived compounds, for example, the antifungal ketoconazole, a CYP3A4 inhibitor, has been reported to increase the peak concentration (Cmax) of THC and its area under the plasma concentration *vs* time curve (AUC) by 1.2 and 1.8 times, respectively, with even more significant increases in the concentration of THC metabolites [9]. Other CYP3A4 inhibitors include, for instance, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole and boceprevir, which may produce similar increases in THC concentrations [10].

On the other hand, one study revealed that rifampicin, a CYP3A4 inducer, reduced approximately 20-40% in plasma THC levels. But in the case of CBD, substrate of CYP3A4 and CYP2C19, ketoconazole increased CBD plasma concentration by about 2 times, while rifampicin reduced those levels by 50% to 60%. Other CYP3A4 inhibitors and inducers are likely to have a similar effect on plasma CBD concentrations if co-administered with it. However, omeprazole, which is a modest CYP2C19 inhibitor, did not change the plasma concentration of CBD [11]. Similar situations are of special concern in cancer patients. The authors mention several aspects to be considered in these cases [10]. If the patients have a liver compromise it is even more problematic.

Although not making part of the scope of the present review, the consumption of recreational Cannabis can still affect the effectiveness of some drugs, but despite everything, some *in vitro* studies indicate that THC and CBD have limited capacity to inhibit the activity of CYP450 enzymes. In our modest point of view, the chronic, and high recreative consume of Cannabis can maybe interchanged the expected outcomes as happen for instance in acute or chronic alcohol consume (the data is still scarce). Despite this, an increased response to warfarin was observed in one patient who smoked 4 to 5 joints per week [12]. Also smoked marijuana, but not oral administration, has been shown to increase the metabolism of theophylline and chlorpromazine, with a reduction of about 50% in their plasma concentrations. This could be due to CYP1A2 induction when smoking more than 2 joints per week. In fact, hemostasis has a delicate balance between coagulation and the fibrinolytic system to achieve a normal blood circulation. Some authors highlight the links connecting cannabinoid actions with blood coagulation abnormalities, suggesting crosstalk between the coagulation system and the endogenous cannabinoid system [13].

Meanwhile, pending further studies, patients taking THC should be advised to avoid drugs that alter CYP3A4 and CYP2C9 activity, such as amiodarone, cimetidine, cotrimoxazole,

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fluoxetine, fluvoxamine, fluconazole, metronidazole and voriconazole, which may inhibit these isoenzymes.

The Tables throughout the next sections, establish a relationship between several possibilities of interactions for cannabinoids and drugs used in the selected pathologies which are currently recognized as being ameliorated with cannabinoids prescription. They will provide some highlights to evaluated expected the impact of the association, afterwards, previously to follow-up processes.

Assessing the potential for interaction should be carried out in both directions, i.e. both cannabinoids on other drugs, as well as the effects of other drugs on cannabinoids or their derivatives.

To achieve a successful and safe therapy, prior assessment of the impact of interactions that may occur is recommended, especially in clinical personalized cases. As an effective support in clinical practice, this work summarizes the available data (clinical and non-clinical) that currently scientifically validate the pharmacological interactions between cannabinoids and other active molecules and vice-versa. Despite the scientific and clinical evidence, the assessment of plasma concentrations of cannabinoids, as well as the other drugs with which they are co-administered, should tend to become a current practice for greater effectiveness of personalized treatments.

To avoid all the above-cited possible situations, which are probable to compromise the well-being of the patient, it is crucial to talk with a healthcare provider before using any medication in combination with cannabinoids, as they can advise on the potential risks and benefits. They may also suggest alternative treatments or adjust the dose of the medication to minimize any potential interactions. This work compiles, for the first time, the data, our personal experience with patients and practical suggestions that can be used as a clinical approach to this adjuvant therapeutic.

2. Results

Detailed evaluation of potential interactions in adjuvant therapy with cannabinoids were provided for the selected pathologies where cannabinoids have been approved, and/or can be used off the label in benefit for patients. Selected chronic diseases include Epilepsy, Autism Spectrum Disorder (ASD), Oncology, Multiple Sclerosis and Chronic Pain.

2.1. Epilepsy

The pharmacological interactions of cannabinoids in the treatment of drug-resistant epilepsy both in the adult population and in children are potentially predictable. However, many gaps remain without information and future clinical trials should be consider.

Regarding the Pediatric Population for the treatment of children aged at least two years old and diagnosed with Lennox-Gastaut Syndrome or Drave Syndrome, CBD was, in 2018, approved in the USA and in 19 September of 2019 in European Union. The recommended starting dose is 2.5 mg/kg twice daily (5 mg/kg/day) for one week, followed by an initial maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). However, slower dose escalation may be warranted, taking 3-4 weeks to reach 10 mg/kg/day. After evaluating the response, clinicians may increase the dose by 2.5 to 5 mg/kg twice daily in weekly increments as needed to achieve clinical effect. The drug Epidyolex® (1000 mg/mL) is a liquid formulation of CBD in sesame oil (flavored). It is indicated in combination with clobazam to treat patients from the age of two with Lennox-Gastaut syndrome or Dravet syndrome. It is also prescribed to treat tuberous sclerosis complex with other epilepsy treatments in patients aged two years and older. These are rare types of epilepsy that start in childhood and can continue into adulthood. Symptoms of these conditions include various types of seizures, learning difficulties, and behavioral problems. These conditions are rare and Epidyolex® has been designated as an “orphan medicine” by EMA (https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex).

A double-blind, randomized clinical trial that included 120 children and young adults with Dravet syndrome and drug-resistant seizures, demonstrated that oral administration of CBD (20 mg/kg/day) concomitantly with already instituted pharmacotherapy decreased the frequency of

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seizures (*vs* placebo), but increased the incidence of adverse effects (diarrhea, vomiting, fatigue, pyrexia, drowsiness and changes in liver function) [4]. The same study highlighted clobazam (65%), valproic acid (AVA)/valproate (59%), stiripentol (42%), levetiracetam (28%) and topiramate (26%) as the most frequently co-administered drugs. It even showed that the most common adverse event was drowsiness (n=22, 36%, in the CBD group and n=6, 10% in the placebo group), and, among the 22 patients enrolled in the CBD group, 18 were undergoing treatment also with clobazam. The CBD dose was reduced in 10 patients, and adverse events were completely reversed in 8 of them. Liver changes, namely the increase in transaminase levels (alanine aminotransferase and/or in aspartate aminotransferase), which was approximately 3-fold above the upper limit of the normal range, led to the withdrawal of 3 patients from the CBD group and 1 from the placebo group. Overall, elevated levels of aminotransferases occurred in 12 patients in the CBD group (*vs* 1 in the placebo group), all of whom were also taking AVA/valproate.

In this context, and because CBD is metabolized by CYP2C19 and CYP3A4, which are induced (eg, AVA/valproate) or inhibited by various antiseizure drugs (eg, carbamazepine, topiramate and phenytoin), pharmacokinetic clinical studies have been carried out with pediatric patients. CBD is also described as an inhibitor of CYP3A4 and the CYP2C family, and the consequent impact on the clinical response can be unpredictable. Among them, clinical trial NCT02324673 stands out, enrolling 61 pediatric patients (1-17 years old) with drug-resistant epilepsy and administered with CBD as an add-on therapy [13] . The clinical trial aimed to evaluate the pharmacokinetics and short-term tolerability of CBD, determining its plasma concentrations as well as the concentration of its active metabolite, the 7-hydroxyCBD (7-OH CBD). The study showed that systemic exposure to CBD increases linearly with the increment of the administered dose. No statistically significant differences were detected between children and adolescents. However, the influence of clobazam on the AUC and the Cmax of CBD was evidenced. Thus, patients treated with CBD (40mg/kg/day) and clobazam had a mean value of systemic exposure 10 times higher than that of patients who did not receive clobazam (AUC: 3130 ng·h/mL *vs.* 1245 ng·h/ mL), while Cmax was approximately 2.4 times higher. Likewise, a trend towards increased 7-OH CBD concentrations was observed with clobazam administration (approximately 3.06-fold higher Cmax and 3.14-fold higher AUC). Furthermore, CBD appeared to increase clobazam and norclobazam (N-CLB) concentrations in a dose-dependent manner: on day 10, mean plasma concentrations of clobazam increased 1.7- and 2.2-fold in patients co-administered with CBD (40 mg/day). kg/day) compared to 10 mg/kg/day and 20 mg/kg/day (857 ng/mL vs. 500 ng/mL and 390 ng/mL), respectively. Similarly, the mean of N-CLB plasma concentrations were also higher in patients treated with this compound at 40 mg/kg/day compared to 20 mg/kg/day and 10 mg/kg/day (6111 ng/mL vs. 4750 ng/ mL and 3224 ng/mL, respectively).

The bidirectional interaction between these two drugs is also evident in children and adolescents, because both are substrates for CYP3A4. The significant inter-individual variability observed in the study led the authors to recommend the monitoring of serum concentrations of both drugs, together with their clinical monitoring.

These results were corroborated by another clinical trial evaluating the pharmacokinetics of CBD in children with Dravet Syndrome aged between 4-10 years [14]. In addition to linear pharmacokinetics, pharmacokinetic interaction with clobazam at the 3 doses of CBD (5, 10 and 20 mg/kg/day) was characterized by increased plasma exposure of N-CLB, which may contribute to antiseizure therapeutic effects and adverse effects (sedation, fatigue), even though additional sedation was not reported in this study. Interestingly, the increase in N-CLB was not observed in the presence of stiripentol, suggesting that stiripentol greatly inhibited CYP2C19, although additional evidence is needed as the sample size in the study was limited to 4 patients.

A broader essay was carried out to help the understanding of the mechanistic target of Rapamycin inhibitors, everolimus and sirolimus which have activity against epilepsy, multiple manifestations of tuberous sclerosis complex and are also approved to treat astrocytomas, angiomyolipomas and lymphangioleiomyomatosis. Nevertheless, once again there is a lack of information regarding drug-drug interactions between mechanistic target of rapamycin inhibitors and, for instance, CBD in clinical practice. The authors reviewed special chosen patients, with

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tuberous sclerosis complex, under treatment with a mechanistic target of rapamycin inhibitor (everolimus, sirolimus) and CBD. Clinical information, mechanistic target of rapamycin inhibitor and CBD dosing, concomitant antiseizure drugs, as well as laboratory and adverse events were reviewed before and after initiation of this cannabinoid. A total of 25 patients were treated and a mechanistic target of rapamycin inhibitor (18 everolimus, 7 sirolimus) and CBD was evaluated. All mechanistic targets of rapamycin inhibitor levels were strained as troughs. Levels were significantly higher in 76% patients after CBD treatment (P = 0.0003). Median change from baseline was +9.8 ng/mL for everolimus and +5.1 ng/mL for sirolimus. About 40% of the patients presented side events, diarrhea being the most frequent (3 patients. No severe adverse events happened during the treatment period. Important data include the fact that CBD increased serum levels of everolimus and/or sirolimus. Some patients experienced doubling or tripling of their mechanistic target of rapamycin inhibitor trough after CBD it was administered. In some cases, clinical toxicity was observed, as well as laboratory abnormalities. Awareness of this interaction can lead clinicians to evaluate serum levels and other safety laboratory studies more closely, and thereby avoid potentially significant adverse effects. In patients known to be disposed to mechanistic target of rapamycin inhibitor toxicity, preventive reduction in dose may be warranted upon initiation of CBD[15].

Table 1 exhibits the most common drugs used in clinical management of epilepsy and the possible outcomes expected when both cannabinoids, CBD and THC, are concomitantly used.

2.2. Autism Spectrum Disorder (ASD)

Today, there are more and more children, and even adults, diagnosed with ASD. For instance, in 2023 data published reveal an increase in prevalence with 1 in 36 children or over 2.7% of 8-year-old children diagnosed with an ASD in 2020, and for the first time reveals higher prevalence rates among Black non-Hispanic, Hispanic, and Asian or Pacific Islander children compared to White non-Hispanic children. In this study the authors also found that males had higher prevalence compared with females regardless of intellectual disability status (https://www.cdc.gov/ncbddd/autism/data.html; assessed January 30th, 2024).

The first-line stimulant drugs are methylphenidate and lisdexamfetamine followed by the second-line non-stimulant atomoxetine. The main pharmacological effects of these drugs are the inhibition of dopamine and noradrenaline transporters, increasing the concentration of these neurotransmitters in the synaptic clefts. In this way, there is a decrease in the characteristic symptoms of the disease, improving the quality of life of the patients. These drugs are liable to suffer and/or generate interactions, requiring a careful evaluation during the clinical process.For methylphenidate, interactions via CYP450 enzymes are not as problematic since it is not metabolized through this mechanism. However, for example, risperidone or lisdexanmfetamine, whose metabolic pathway use CYP2D6, an interaction with CBD is expected to occur as it inhibits CYP2D6. Therefore, there is an increase of plasma concentrations of risperidone and lisdexamfetamine [16].

Table 1. Clinical evidence of the potential of CBD developing pharmacokinetic/pharmacodynamic interactions with antiseizure drugs (ASDs). Highlighted with green are clinical accepted interactions; highlighted with yellow are interactions scarcely investigated in clinical practice but with high potential in theory to compromise ASD efficacy and safety.

Antiseizure drugs	Evidence type*	Pharmacokinetic interactions			Pharmacodynamic interactions			
		CBD effect on the ASD	ASD effect on CBD	Mechanism of interaction	Therapeutic effect	Adverse effects	Mechanism of interaction	Clinical recommendations
Valproic acid (AVA)	POCS [13,14,17]	↔ Cp	NR	CBD inhibits UGT1A9/2B7 that metabolizes AVA.	↑ in preclinical animal models	↑ transaminase levels	Interactions at mitochondrial level	Monitoring transaminase levels. ↓AVA dose or withdraw CBD** [18]
	RCT [19–21]	↔ Cp ↓Plasma Cmax and AUC of AVA ↔ LPP	↔ [CBD] ↑ [7-OH-CBD] ↔LPP	NR	[7-OH-CBD] ↑ but not clinically relevant	NR	NR	
Brivaracetam	POCS	↑ Cp > MT	NR	CBD inhibits CYP2C19 which metabolizes the ASD.	NR	NR	-	↓ brivaracetam dose
Carbamazepine (CBZ)	POCS	↔ Cp	NR	CBZ induces CYP3A4 and CYP2C19, with potential ↓[CBD]	NA	NA	-	↑ CBD dose or ↓ CBZ dose ASDs therapeutic monitoring is advisable
Clobazam (CLB)	Coorte observational study	↑ [N-CLB]	↑ [CBD] ↑ [7-OH-CBD]	CBD inhibits CYP2C19, responsible for N-CLB inactivation; CLB inhibits UGTs, CYPs and ↑ [7-OH-CBD]	Potentiated due to the interaction	Drowsiness, sedation, lethargy (related to [N-CLB].	$GABA_A$-R	ASDs monitoring is strongly recommended. transaminases and bilirrubin must be monitored**. ↓CLB dose or CLB withdraw [18]
	RCT	↑ [N-CLB]	↑ [7-OH-CBD]	-	-	-	-	

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Antiseizure drugs	Evidence type*	Pharmacokinetic interactions			Pharmacodynamic interactions			
		CBD effect on the ASD	ASD effect on CBD	Mechanism of interaction	Therapeutic effect	Adverse effects	Mechanism of interaction	Clinical recommendations
Clonazepam	POCS	↔	NR	NR	-	-	-	Without clinical evidence of interaction.
Eslicarbazepine (active metabolite of the prodrug eslicarbazepine acetate)	POCS	↑ Cp linearly as CBD dose ↑; ↔ MT	NR	The excipient sesamine inhibits eslicarbazepine glucoronidation	No clinical relevant changes	No clinical relevant changes	-	More studies are required. Careful and report of interaction are required.
Ethosuximide (ETX)	POCS	↔	NR	ETX is metabolized by CYP3A4, which is inhibited by CBD.	-	-	-	Without clinical evidence but ↓ ETX dose may be considered
Felbamate (FLB)		↑ Cp	↓↑ Cp	FLB induces CYP3A4 and inhibits CYP2C19, which metabolize CBD. CBD inhibits CYP3A4, which is responsible for FLB metabolism.				CBD therapeutic monitoring is strongly recommended. ↓ FLB dose
Fenfluramine	Unpublished data on file (Zogenix)	↔	↔	-	NR	NR	NR	Without clinical evidence of interaction.
Lacosamide	POCS	↔ Cp	↑ [CBD] pre-clinical (animal evidence)	Lacosamide inhibits CYP2C19, CYP3A4 and CYP2C19	↔	↔	-	CBD should ideally be monitored.

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Antiseizure drugs	Evidence type*	Pharmacokinetic interactions			Pharmacodynamic interactions			
		CBD effect on the ASD	ASD effect on CBD	Mechanism of interaction	Therapeutic effect	Adverse effects	Mechanism of interaction	Clinical recommendations
Lamotrigine (LAM)	POCS	↔ Cp	Mice model: ↔	CBD inhibit UGT1A4 and UGT2B7; Cp of LAM effect did not had a significant change	Mice model: ↔			Without clinical evidence of interaction.
Levetiracetam	RCT	↔ Cp	NR	NR	NR	NR	NR	Without clinical evidence of interaction.
Midazolam		↑ ative metabolite (1-OH-midazolam)	NR	NR				Midazolam should be monitored
Oxcarbazepina (OXC)	POCS	↔ Cp ↑ Cp (preclinical mice model)	Mice model: OXC ↑ uptake of CBD to the brain CBD Cp ↓ beacuse OXC induces CYP3A4	Mice model: CBD inhibits UGTs that conjugate the active metabolite of OXC.	NR in humans Mice model: CBD increases the therapeutic effect of OXC.	-	-	More clinical studies are required. Careful and report of interaction are required
Perampanel (PER)	POCS	↔Cp, but in theory, Cp can be increased	NR	CBD inhibits CYP3A4 which metabolizes PER.	NR	NR	-	Therapeutic drug monitoring is advisable because PER has a narrow MT [12]
Phenobarbital	POCS	↑ Cp	Phenobarbital induces CYP3A4 and CYP2C19,	CBD inhibits CYP2C8/9 and CYP2C19, which metabolizes	Preclinical animal studies	NR	-	↑ CBD dose or ↓ phenobarbital dose.

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Antiseizure drugs	Evidence type*	Pharmacokinetic interactions			Pharmacodynamic interactions			
		CBD effect on the ASD	ASD effect on CBD	Mechanism of interaction	Therapeutic effect	Adverse effects	Mechanism of interaction	Clinical recommendations
			↑ [CBD]	phenobarbital.	evidence no interactions.			
Phenytoin (PHT)	POCS	↔ Cp	NR	CBD inhibits CYP2C19, which metabolizes PHT.	NR	NR	-	PHT has narrow MT. PHT therapeutic monitoring is strongly recommended.
Primidone		↓ Cp						
Rufinamide	POCS [22]	↑ Cp linear with CBD dose ↔ MT	Inhibition of carboxyl-esterases by sesamine		NR	Not observed	NR	Changes are not clinically relevant.
Sirolimus	ROCS[23,24]	↑ Cp (2-3 fold)	NR	CBD inhibits CYP3A4, which metabolizes mTOR inhibitors.	NR	NR	-	Therapeutic drug monitoring is advisable for mTOR inhibitors.
Everolimus	Case report [24]	↑↑ Cp			-	-	-	
Stiripentol (STP)	RCT	↑ Cp [14,25] ↔ Cp [21]	↑ [CBD][13] ↓ [7-OH-CBD] ↓ [7-COOH-CBD] [14] ↔[N-CLB] when CLB is coadministered with CBD	STP Cp ↑ because CBD inhibits CYP2C19 [14] STP inhibits CYP3A4 and CYP2C19, decreasing CBD Cp.	NR	NR	NR	Therapeutic drug monitoring is advisable because STP has narrow MT Clinical relevance is scarce, requiring more studies.

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Antiseizure drugs	Evidence type*	Pharmacokinetic interactions			Pharmacodynamic interactions			
		CBD effect on the ASD	ASD effect on CBD	Mechanism of interaction	Therapeutic effect	Adverse effects	Mechanism of interaction	Clinical recommendations
Topiramate (TPR)	RCT [21][	↔ Cp	↑ Cp Mice model: CBD Cp ↑ in plasma and brain [26]	TPR inhibits CYP2C19 and induces CYP3A4[26,27]	Mice model: CBD activity ↑[26]			Ttherapeutic monitoring of TPR and its side effects are strongly recommended [28]
	POCS [29]	↑ Cp	Higher power test of POCS justifies differences to RCT		No clinical relevant changes [22]	-	-	
Vigabatrine	POCS[12,22]	↔Cp	NA	-	NR	NR	-	Without clinical evidence of interaction
Zonisamide	POCS [22,29]	↑ Cp linearly as CBD dose ↑. ↔ MT	↑ [CBD] ↑ [7-OH-CBD] [18]	CBD inhibits CYP3A4 that metabolizes zonisamide.	↔	NR	-	Without clinical evidence of interaction

* POCS, Prospective observational clinical study; RCT, Randomized clinical trial; Pre-clinical; ROCS, Retrospective observational coorte study. ** Transaminases > 3x ULN and bilirrubin > 2x ULN; or Transaminases > 5x ULN [5]. ? uncertain; >, superior; < lower; ↑ increase; ↓ decrease; ↑↓ variability; Cp, plasma concentration; $GABA_AR$, type A receptor of Gamma-aminobutyric acid; mTOR, mechanistic target of rapamycin NR, not reported; PPB, plasma protein binding; TR, therapeutic range; ULN, upper limit of normal .

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Meanwhile, FDA-approved indications for oral risperidone (tablets, oral solution, and M-TABs) include the treatment of schizophrenia (in adults and children 13 years of age and older), acute manic episodes, or mixed bipolar as monotherapy (in adults and children aged 10 years and older), adjunctive bipolar or acute manic or mixed episodes with lithium or valproate (in adults), and irritability associated with autism (in children aged 5 years and older). In addition, long-acting risperidone injection is approved for use in schizophrenia and bipolar disorder maintenance (as monotherapy or adjunct to valproate or lithium) in adults. Therefore, there are varied non-FDA approved uses for risperidone. This describes the indications, mechanisms of action, methods and routes of administration, significant adverse effects, contraindications, and monitoring of risperidone so that practitioners can direct patient therapy toward treating conditions for which it is indicated as part of the team interprofessional.

All antipsychotics have some degree of antagonism at D2 receptors. First-generation antipsychotics produce antipsychotic effects at 60% to 80% of D2 occupancy. Second-generation antipsychotics, such as risperidone, exhibit their therapeutic effects through some D2 blockade, but more through blockade of serotonin receptors such as 5HT2A. Second-generation antipsychotics are loosely bound to D2 receptors and can rapidly dissociate from the receptor, possibly making them less likely to cause extrapyramidal symptoms (EPS). In addition, second-generation antipsychotics exhibit 5HT1A receptor agonism. Serotonin and norepinephrine reuptake inhibition are potential mechanisms by which risperidone is postulated to produce antidepressant effects. It is believed that the improvement of positive symptoms is achieved by blocking D2 receptors, specifically in the mesolimbic pathway. The ability of antipsychotics to block D2 receptors in the prefrontal cortex and *nucleus accumbens* is essential for improving certain psychiatric symptoms. Importantly, risperidone does not cause anticholinergic effects, which may benefit patients in certain populations, including elderly people with dementia [30]. All those evidences require a special care if other drugs target the same receptors.

There is experimental evidence that CBD induces anxiolytic and antiseizure effects through the activation of 5-HT1A receptors (receptors coupled to Gi/o proteins and induce inhibitory effects). Currently, the interaction of CBD with 5-HT1A receptors in the human brain is unknown. However, the fact that risperidone and CBD can compete for the same receptors needs to be evaluated. Indeed, experimental evidence indicates a decline in 5-HT1A receptor binding in the brain of patients with epilepsy which may make this association even more impressive.

2.3. Oncology

Emerging evidence suggests positive results from the use of cannabinoids associated with cancer treatments. Some authors explore the possibility of therapeutic synergy [31] but mostly of the times, the assessment of possible drug-drug interactions which compromise the treatment efficacy are not discussed. The specific clinical trials that could validate these possibilities are scarce, and most of them include mixes in different ratios of CBD and THC, not for improve of the chemotherapy itself but only to relieving symptoms inherent to the pathology, such as insomnia, nauseas, pain or some other side effects.

In preclinical studies, CB1 and CB2 agonists (i.e. anandamide and THC) showed to inhibit the proliferation of HR+ breast cancer cell lines. However, in animal models there is no relevant evidence to that can leverage new clinical trials. Nevertheless, there is data regarding the action of cannabinoids on the hormones of the hypothalamic-pituitary-gonadal axis. Two of the studies observed, in healthy premenopausal women, a positive correlation between the plasma peak of the endogenous cannabinoid anandamide with the plasma peak of 17β-estradiol (luteinizing hormone) and follicle-stimulating hormone levels at ovulation. This evidence questions the possibility of an effect of cannabinoids on hormone receptor positive (HR+) breast cancer [32].

Due to the scarce information, as it was described above for the previous pathologies where cannabinoids can be coadministered with other drugs, possible interactions will be discussed also for oncological treatments. For instance, the simpler situation involves the fact that there are several antitumor drugs which use the same metabolic pathway, such as CYP3A4, and the

 doi:10.20944/preprints202402.0458.v1

concomitant intake of cannabinoids, or Cannabis flower extracts, and/or drugs containing cannabinoids may compromise the efficacy and safety of the protocol therapy (eg, Anastrazol, Imatinib, Paclitaxel, Sunitinib, Tamoxifen, Trabectedin, etc. see Table 2).

The results from two studies have shown that Tamoxifen, and several other estrogen receptor modulators, can act as inverse agonists at CB1 and CB2 receptors, resulting in an interaction with possible clinical consequences. In addition, cannabinoids can interact with other drugs, endocrine and targeted therapies, used in this type of oncological treatments [32].

However, as exemplified above, there is still a gap to fill in relation to assess the risk of potential interactions between the various drugs used in this context. Table 2 identifies the most used chemotherapy drugs and possible plasma concentration changes induced by cannabinoids.

Other drugs associated to the therapeutic protocols (ea., corticoids, analgesics, anxiolytics and antidepressant drugs), which induce or inhibit these pathways, can also increment this bias. In an ideal treatment each patient should have the plasma concentration of cannabinoids and the antitumor drugs evaluated careful allover the time to avoid risks of failure or side effects.

For instance, in the case of bone-only metastatic disease, the treatment is addressed with initial sequential hormone therapy, Drugs as Abemaciclib, Palbociclib and Ribociclib were under evaluation in a Phase 1, multicenter, open-label, fixed-sequence study (NCT02688088) conducted in patients with advanced and/or metastatic cancer. Abemaciclib use the pathway of CYP3A4 for elimination, and the authors performed the essays with Rifampin (strong CYP3A inducer) and clarithromycin (a strong CYP3A inhibitor). The enrolled patients were at least 18 years of age with an Eastern Cooperative Oncology Group (ECOG) score between 0 and 2 and adequate organ function. The majority of the 44 patients enrolled were Caucasian (91%) with a mean age of 60 years (range: 37–78 years) The patients who had surgery performed that could affect the absorption or experience emesis that may affect drug PK, were exclude. The validated Cooperstown 5+1 cocktail was administered orally as a single dose or on two occasions; it was constituted by 0.2 mg of midazolam (CYP3A4), 10 mg of S-warfarin (CYP2C9), 30 mg of dextromethorphan (CYP2D6) and 100 mg of caffeine (CYP1A2). Data from caffeine and paraxanthine (metabolite) presented bias due to the confounding effect of dietary consumption. The main conclusion showed by the authors was a no clinically relevant change in the pharmacokinetics of substrates of CYP1A2, CYP2C9, CYP2D6, or CYP3A drugs when coadministered with multiple doses of abemaciclib. This lack of translation should be replicated for the most relevant drugs, since it suggests that the CYP mechanisms of downregulation *in vitro* need to be improved and understood [33]. The relevance of this Clinical Trial where to allow the discussion among these types of drug-drug interactions. Although further research is needed, specifically for the topic that we are writing about, this data is relevant. The crucial dose of cannabinoids which will be recommended co-administered with the drugs, commonly prescribed in different types of cancers still leaves the doctors waiting for the best final result of this co-therapy.

A random prospective double-blind study to evaluate the effectiveness of nabilone, a synthetic cannabinoid, compared to Prochlorperazine involved eighty patients in chemotherapy regiment and where most of them received Cisplatin, a drug that universally produces severe nausea and vomiting. The patients received either nabilone or prochlorperazine during two consecutive treatment courses with the identical chemotherapy. Prochlorperazine, also known as Compazine (brand name), is a piperazine phenothiazine and first-generation antipsychotic drug that is used for the treatment of severe nausea and vomiting. Side effects consisting of hypotension and lethargy were more pronounced with nabilone. Sixty patients (75 %) reported nabilone to be more effective than prochlorperazine for relief of nausea and vomiting. Of these 60 patients, 46 required further chemotherapy and continued taking nabilone as the antiemetic of choice. [34]

Nabilone was also enrolled in another study that showed evidence of antiemetic efficacy in chemotherapy with cyclophosphamide. All patients received two 21-day cycles of combination chemotherapy comprising Cyclophosphamide (CTX) 1 g/m(2), Adriamycin (ADR) 40mg/m(2) and Etoposide (VP 16) 1OOmg/m(2) on Day 1; VP 16 lOOmg/m(2) on Days 2 and 3; and Vincristine 2mg with Methotrexate 50mg /m(2)on Day 10, followed by folinic acid rescue. The Day 1-3 chemotherapy pulses were given on an in-patient basis, with CTX and ADR administered as i.v.

 doi:10.20944/preprints202402.0458.v1

boluses and VP-16 as an i.v. infusion over 1-2 h. Of the 34 patients entered, 6 dropped out after the first course (5 died during the first cycle of chemotherapy, one was withdrawn from chemotherapy after review of histology), and 2 patients did not complete a course because of adverse effects, leaving 26 patients who completed the crossover. Four of these entered the study on their first cycle of chemotherapy and received one prior cycle with standard phenothiazine antiemetics and had all experienced mild to moderate gastro-intestinal toxicity and so were considered suitable for inclusion in the analysis. with Cyclophosphamide, Adriamycin and Etoposide. Symptom scores were significantly better for patients on nabilone for nausea, retching and vomiting (P less than 0.05). Fewer subjects vomited with nabilone (P = 0.05) and the number of vomiting episodes was lower (P less than 0.05); no patients on nabilone required additional parenteral antiemetic. More patients preferred nabilone for antiemetic control (P less than 0.005). Adverse effects common with nabilone were drowsiness (57%), postural dizziness (35%) and light-headedness (18%). Euphoria was seen in 14% and a "high" in 7%. Erect systolic blood pressure was lower in nabilone patients on Day 1 (P = 0.05) but postural hypotension was a major problem in only 7%. Nabilone was considered an effective oral anti emetic drug for moderately toxic chemotherapy, but the range and unpredictability of its side effects warrant caution in its use.[35]

Paclitaxel (PAC) is associated with chemotherapy-induced neuropathic pain (CIPN) that can lead to the cessation of treatment in cancer patients even in the absence of alternate therapies. This drug is metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8, and to two minor metabolites, as 3′-*p*-hydroxypaclitaxel and 6α, 3′-*p*-dihydroxypaclitaxel, by CYP3A4. It was previously reported that chronic administration of the non-psychoactive CBD prevents PAC-induced mechanical and thermal sensitivity in mice. Hence, researchers pursued to determine receptor mechanisms by which CBD inhibits CIPN and whether negatively effects nervous system function or chemotherapy efficacy. The ability of acute CBD pre-treatment to prevent PAC-induced mechanical sensitivity was assessed, as was the effect of CBD on place conditioning and on an operant-conditioned learning and memory task. Added information was obtained by using the MTT assay to determine the potential interaction of CBD and PAC on breast cancer cell viability. PAC-induced mechanical sensitivity was prevented by administration of CBD (2.5 – 10 mg·kg−1) in female C57Bl/6 mice. This effect was reversed by co-administration of the 5-HT1A antagonist WAY 100635, but not with the CB1 antagonist SR141716 or the CB2 antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory. Also, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability. This data suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT1A receptor system. Additionally, CBD treatment was lacking of conditioned rewarding effects or cognitive impairment and did not attenuate PAC-induced inhibition of breast cancer cell viability. Despite the essay's needing further investigation in humans, this preliminary data indicates that adjunct treatment with CBD during PAC chemotherapy could be safe and effective in the prevention or attenuation of CIPN [36].

Inhibition of estrogen action at the target tissue level with the antiestrogen, Tamoxifen, has proved highly successful in the treatment of hormone-responsive breast cancer. Notwithstanding its proven effectiveness, forty percent of patients eventually discontinue Tamoxifen therapy early, mainly due to side effects such as hot flashes, arthralgia, insomnia, and mood alterations. This is a prodrug metabolized mostly by the isoenzyme CYP2D6 in its main and most active metabolite endoxifen. Due to the complex metabolism, Tamoxifen is disposed to to drug-drug or drug-herb interactions. It is, therefore, expected that CBD might also affect Tamoxifen pharmacokinetics since it is known to be a potential inhibitor of CYP2D6. To get an idea of how this process could be affected, an investigation was carried out enrolling a total of 35 patients to determine the pharmacokinetic interaction between CBD-oil and endoxifen. Four patients were excluded before the start of the study due to voluntary withdrawal (N = 2), disease progression (N = 1), and an endoxifen level <16 nM despite dose escalation (N = 1). Five others were excluded during the study due to protocol violation (N = 3), personal circumstances (N = 1), and poor venous access for blood withdrawal (N = 1). There were 26 evaluable patients whereof 15 for the primary pharmacokinetic endpoint. The study started with continuation of Tamoxifen monotherapy for 7 days. Patients took

 doi:10.20944/preprints202402.0458.v1

Tamoxifen at 9 am and were then hospitalized for 24h pharmacokinetic blood sampling of the prodrug and also the active metabolite endoxifen. The dose started with 5 drops 10% CBD-oil sublingually three times daily for four weeks (i.e., ≈50 mg CBD per day, the highest over-the-counter dose) concomitantly to their Tamoxifen treatment. The pharmaceutical grade CBD-oil was manufactured by a Dutch Pharmacy (Clinical Cannabis Care, Breukelen, the Netherlands, article number 16779517). After four weeks of concomitant CBD and Tamoxifen, patients were again hospitalized for pharmacokinetic blood sampling. The data provide from this study allowed to conclude that hot flashes and arthralgia improved with at least one grade in six out of 25 patients (24%) and insomnia improved with one grade in 11 out of 26 patients (42%). This is in line with the trend seen in improvement in separate endocrine subscale items. Ten out of 26 patients (38%) experienced CBD-oil related toxicity. Most frequented mentioned side effects were fatigue (N = 3, 12%) and dry mouth (N = 3, 12%). All side effects were grade 1. None of the patients quit CBD-oil because of side effects and sixty-nine percent of patients wished to continue CBD-oil after the study was finished [37].

In another study, in this case with temozolomide (TMZ), phase I and II, scientists evaluated the influence of administration of Sativex in patients with already temozolomide treatment for glioblastoma. This drug is quickly absorbed after oral intake and undergoes non-enzymatic hydrolysis into its active metabolite 5-(3-metiltriazeno1-il) imid-azol-4-carboxamida (MTIC) and renal excretion of the base drug. After oral administration, approximately 5% of dose is recovered unchanged in the urine within 24 hours and the remainder of the recovered C^{14} is excreted such as 5-aminoimidazole-4-carboxamide (AIC), temozolomide carboxylic acid (TMA) or unidentified polar metabolites. The ratio of blood to plasma radioactivity concentrations increased after 12 h after administration of post-^{14}C-TMZ. This study, has in phase I two parts: first, six patients received a personalized regime of Sativex of up to 12 sprays per day (side effects reported were fatigue, headache, vomiting and nausea); in the second, 21 patients randomly received during 12 months Sativex with temozolomide (12 patients) or placebo with temozolomide (9 patients). After one year, 10 out of 12 of the patients receiving Sativex were still alive and 4 out of 9 patients who were given a placebo were still alive to. However, two patients in the placebo arm died within 40 days of enrolling (these patients may have been predisposed to a shorter survival due to features of their tumour). The data provide from these events indicated that Nabiximols (trade name Sativex) could be tolerated by patients in combination with chemotherapy. Then, phase II trial three-year phase II trial (ARISTOCRAT), funded by The Brain Tumour Charity and co-ordinated by the Cancer Research UK Clinical Trials Unit at the University of Birmingham, is due to begin recruiting more than 230 patients across all UK nations in early 2022. This trial was set up for patients who have got aggressive glioblastoma and that have grown back after first line treatment. They also need to have the subtype of glioblastoma that is sensitive to temozolomide. Among the inclusion criteria, the patients should be postmenopausal women according to standard clinical criteria or receiving concomitant luteinizing hormone-releasing hormone (LHRH) agonist therapy, they must take aromatase inhibitor therapy (anastrozole, exemestane, or letrozole) for adjuvant treatment of breast cancer or for chemoprevention for at least 3 weeks and no more than 2 years at the time of enrollment. In this new phase II trial (registrated at 25/10/2022 and last edited in 31/08/2023), a randomized placebo-controlled double-blind parallel-group study, researchers will assess whether adding Sativex to the current standard chemotherapy treatment (temozolomide) could offer extra time to live for adults diagnosed with a recurrence of their glioblastoma after initial treatment. Even, the authors do not mention the possible evaluation of possible drug-drug interactions we expect, that from the collected data, relevant informations which will help to propose, in a near future better treatments use this association of drugs.

The real-life settings with clinical relevance should be publish because they will provide evidences, someimes difficult to obtain in clinical trials. Between some them Guedon et al. described out puts from an oncology day-hospital, with a cross-sectional study in 363 cancer patients treated with chemotherapy where 20 consumed CBD.. Among all patients they described 90 interactions with 34 medicines. The main clinical risks were central nervous system depression and hepatoxicity. The main interactions were considered as moderated and anticancer treatment

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do not seem to be in risk. Neverthless they did the CBD discontinuation has it was a consistent management. This data help to found proves for further studies which provide more robust information on these clinical drug interactions with CBD in cancer patients[38] .

Despite, the results highlighted in this text , we wait with expectation for the data of the various Clinical Trials Phase 2, as described above but also the one with Epidiolex for Treatment of Aromatase Inhibitor-Associated Arthralgias (ClinicalTrials.gov Identifier: NCT04754399). The estimated study completion date was November 2023, but no results are available yet. The design of the study involves the oral solution of CBD, which is given 2x daily. week 1: 25 mg twice daily, approximately 12 hours apart, with food week 2: 50 mg twice daily, approximately 12 hours apart, with food week 3: 75 mg twice daily, approximately 12 hours apart, with food week 4+: 100 mg twice daily, approximately 12 hours apart, with food.

Meanwhile, the Food Standards Agency (FSA) recommended lowering of daily intake of CBD from 70 mg to just 10 mg.

Table 2. Evaluation and discussion notes of clinical evidence for potential developed interactions with cannabidiol (CBD) and drugs used in Oncology.

Antineoplasic Drug	Evidence type *	Study type	Mechanism of interaction	Clinical outcome	Notes/References
CDK4/CDK6 Inhibitors Abemaciclib (Palbociclib) (Ribociclib)	Clinical	Clinical Trial Phase 1, multicenter, open-label, fixed-sequence study conducted in patients with advanced and/or metastatic cancer	CYP1A2, CYP2C9, CYP2D6, CYP3A substrate drugs	No clinically relevant change in the PK of the selected CYP when coadministered with multiple doses of Abemaciclib	Participants were also asked to refrain from consuming grapefruit juice, Seville oranges, and St. John's Wort during the same time frame. No recommendation about caffeine drinks intake [33] (ClinicalTrials.gov Identifier: (NCT02688088)
Aromatase Inhibitors Anastrozole Exemestane Letrozol (although fulvestrant belongs to the same group, it was not included in this trial)	Clinical	Clinical Trial Phase 2 CBD (Epidiolex) for Treatment of Aromatase Inhibitor-Associated Arthralgias (Arthralgia & Breast Cancer)	Evaluation of the safety and efficacy of CBD treatment in postmenopausal women with aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) due to Anastrazole intake (15 weeks duration)	Investigators are looking to see if patients with joint pain experience an improvement with the concomitant use of CBD.	No Results Posted yet (end of the trial October 2023). Although clinical evidence is scarce for Anastrozole inhibition of CYP 1A2, 2C8/9 and 3A4, the effect of concomitant use with CBD, as perform in this clinical trial, will provide relevant data for future prescribed treatments. (ClinicalTrials.gov Identifier: NCT04754399).

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Antineoplasic Drug	Evidence type *	Study type	Mechanism of interaction	Clinical outcome	Notes/References
Carboplatine **Cisplatin**	Clinical	Prospective study Nabilone (synthetic cannabinoid as an effective antiemetic in patients receiving cancer chemotherapy.	NR	Sixty patients (75 per cent) reported nabilone to be more effective than prochlorperazine for relief of nausea and vomiting. Of these 60 patients, 46 required further chemotherapy and continued taking nabilone as the antiemetic of choice.	[34]
Cyclophosphamide (adjuvant or not with doxorubicin or a taxane)	Clinical	Comparative Study Antiemetic efficacy and toxicity of Nabilone, in lung cancer chemotherapy.	CYP P450 isoforms, CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18, and 2C19	Symptom scores were significantly better for patients on Nabilone for nausea, retching and vomiting (P less than 0.05); fewer subjects vomited (P = 0.05) and the number of vomiting episodes was lower (P less than 0.05); no patients on Nabilone required additional parenteral anti-emetic. More patients	Of the 34 patients entered, 6 dropped out after the first course and 2 patients did not complete a course because of adverse effects, leaving 26 patients who completed the crossover. Four of these entered the study on their first cycle of chemotherapy; they received one prior cycle

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Antineoplasic Drug	Evidence type *	Study type	Mechanism of interaction	Clinical outcome	Notes/References
				preferred Nnabilone for anti-emetic control (P less than 0.005).	with standard phenothiazine anti-emetic and had all experienced mild to moderate gastro intestinal toxicity and so were considered suitable for inclusion in the analysis.[35]
mTOR Inhibitor Everolimus	Clinical	Clinical Study CBD Elevates Mechanistic Target of Rapamycin Inhibitor Levels in Patients With Tuberous Sclerosis Complex)	CYP3A4 metabolism Everolimus is a substrate of CYP3A4 and PgP (phosphoglycolate phosphatase. Three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of Everolimus were the 6 primary metabolites detected in human blood. *In vitro,* Everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan	CBD resulted in increased serum levels of Everolimus.	[39]
Paclitaxel	Pre-Clinical	Pre-Clinical study CBD inhibits Paclitaxel-induced neuropathic pain through 5-HT1A receptors without	Metabolism CYP2C8/9	Paclitaxel-induced mechanical sensitivity was prevented by administration of CBD (2.5 – 10 mg·kg−1) in female C57Bl/6 mice.	CBD + Paclitaxel combinations produce additive to synergistic

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Antineoplasic Drug	Evidence type *	Study type	Mechanism of interaction	Clinical outcome	Notes/References
		diminishing nervous system function or chemotherapy efficacy		This effect was reversed by co-administration of the 5-HT1A antagonist WAY 100635, but not the CB1 antagonist SR141716 or the CB2 antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory.	inhibition of breast cancer cell viability. [36]
Selective estrogen receptor modulators Tamoxifen	Clinical	Clinical Trial CBD-oil as a potential solution in case of severe Tamoxifen-related side effects	Metabolism CYP3A4 e 2D6	None of the patients quit CBD-oil because of side effects and sixty-nine percent of patients wished to continue CBD-oil after the study was finished. The authors suggested that CBD-oil, with a dosage below 50 mg, does not have to be discouraged in patients using it for Tamoxifen-related side effects.	The use of CBD-oil allowed to conclude that hot flashes and arthralgia improved with at least one grade in six out of 25 patients (24%) and insomnia improved with one grade in 11 out of 26 patients (42%). This is in line with the trend seen in improvement in separate endocrine subscale items. Ten out of 26 patients (38%) experienced some kind of CBD-oil related toxicity. Most frequented mentioned side effects were fatigue (n =

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Antineoplasic Drug	Evidence type *	Study type	Mechanism of interaction	Clinical outcome	Notes/References
					3, 12%) and dry mouth (n = 3, 12%).[37]
Temozolomide	Clinical	Clinical Trial Phase I and II (use of the cannabis-based drug Sativex with the current chemotherapy treatment in treating patients with recurrent glioblastoma)	Non-enzymatic hydrolysis of Temozolomide into their active metabolite 5-(3-metiltriazeno1-il) imidazol-4-carboxamida (MTIC). In neutral pH. Then it is secreted by kidneys	This trial is set up for patients who have got aggressive glioblastoma that have grown back after first line treatment. They also need to have the subtype of glioblastoma that is sensitive to Temozolomide	The metabolization was not such related with CYP450 metabolization, so it is not such influenced by interactions with other medication. Plasma protein binding at 1 and 4 h showed mean free fractions of radioactivity of 84%; 12–16% of drug-derived radioactivity was bound to plasma proteins; 1% of the 14C-Temozolomide dose was recovered in the feces and 38% was recovered in the urine over the 360-h collection period.[40]

NR, not reported.

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2.4. Multiple Sclerosis and Pain

Here only the questions related to the symptoms which could be treated also with cannabinoids will be discussed. Treatment for multiple sclerosis is tailored to the specific symptoms of the person and the stage of the disease. Interactions of cannabinoids with other centrally acting drugs will be discussed in the same section once they have similar approaches.

The drugs highlight in Table 3 are current in various conditions and reflect also the information available for a concomitant use with cannabinoids. For example, CBD increases plasma concentrations of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and antipsychotics, compromising their pharmacological effect due to its inhibitory capacity on the CYP2D6 isoform. It also interacts with monoamine oxidase inhibitors (MAOIs) such as tranylcypromine, phenelzine and isocarboxazide, inhibiting their metabolism and consequently increasing the mean residence time and half-life of antidepressant drugs, potentiating and prolonging their adverse effects. Clinical trials exploring pharmacological interactions between cannabinoids and antidepressants are rare or practically non-existent [6]. However, it has been shown in animal models of depression and post-traumatic stress disorder, that co-administration of CBD with the SSRI sertraline has a synergistic effect on the development of cognitive and emotional disturbances (eg., severe anxiety and aggressive behavior) [41]. In fact, sertraline is metabolized by CYP3A4, which is inhibited by CBD, leading to an increase in sertraline plasma concentrations and the development of adverse effects [42]. Therefore, this association should be applied in clinical practice with great care.

Divergently, when administered at subtherapeutic doses concomitantly with CBD, the noradrenergic antidepressant desipramine has an antidepressant effect, suggesting the existence of synergistic mechanism. Despite being preclinical studies, these results show that CBD has antidepressant effects dependent on serotonin levels in the central nervous system.

Moreover, many other antidepressants, namely citalopram, paroxetine, mirtazapine and amitriptyline metabolized by isoforms of the CYP superfamily inhibited by CBD used in co-administration may potentiate its adverse effects (Table 3). For example, amitriptyl is metabolized by CYP2D6, CYP2C19, CYP 2C9, CYP3A4 and CYP1A2 which are inhibited by CBD. Thus, the co-administration of them can intensify adverse effects such as anticholinergic syndrome, QT prolongation and drowsiness[42].

Despite, opioids are frequently prescribed to treat and manage chronic pain, data with the association with cannabinoids is scarce and the clinical and real-world evidence are not robust, which is why they have not been addressed here. Forthcoming high-quality-controlled clinical trials should be compulsory to control the opioid-sparing effect of cannabinoids.

Table 3. Clinical evidence of the potential of canabidiol (CBD) developing interactions with other centrally acting drugs [6,12,41,42] .

Drug	Type of Interaction	Clinical outcome and/or recommendations
Amitriptiline	Antidepressant metabolized by CYP2D6, CYP2C9, CYP2C19, CYP3A4 which are inhibited by CBD.	↑ Cp ↑ adverse effects
Citalopram	Antidepressant metabolized by CYP2C19 (38%), CYP2D6 (31%) e CYP3A4 (31%) which are inhibited by CBD.	↑ Cp ↑ adverse effects
Desipramine	Antidepressant moderate inhibitor of CYP3A, which metabolizes CBD.	↑ CBD Cp ↓ CBD dose should be pondered
Diazepam	Benzodiazepine metabolized by CYP2C19 which is inhibited by CBD.	↑ Diazepam Cp ↓ Diazepam dose should be pondered
Escitalopram	Antidepressant metabolized by CYP2C19 which is inhibited by CBD.	↑ Cp ↑ adverse effects
Fluoxetine (FLX)	Antidepressant metabolized by CYP2C19 and CYP2D6 (31%) which are inhibited by CBD. FLX is a moderate inhibitor of CYP2C19, which metabolizes CBD.	↑ Cp of FLX and CBD ↑ adverse effects ↓ dose of both drugs should be pondered
Fluvoxamine	Antidepressant metabolized by CYP1A2, which is inhibited by CBD. It is a moderate inhibitor of CYP3A4, strong inhibitor of CYP2C19, which metabolize CBD.	↑↓Cp of fluvoxamine ↑ CBD Cp ↓ CBD dose should be pondered Therapeutic monitoring of fluvoxamine is recommended
Haloperidol	Antipsychotic drug that moderately inhibits CYP2C19 which metabolizes CBD	↑CBD Cp ↓ CBD dose should be pondered
Imipramine	Antidepressant metabolized by CYP2C19 and CYP2D6 (31%) which is inhibited by CBD.	↑ Cp ↑ adverse effects ↓ imipramine dose should be pondered

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Drug	Type of Interaction	Clinical outcome and/or recommendations
Lorazepam	Benzodiazepine drug metabolized by UGT2B7, which is inhibited by CBD.	↑ Cp ↑ somnolence adverse effect ↓ lorazepam dose should be pondered
Mirtazapine	Antidepressant drug metabolized by CYP1A2, CYP2D6 and CYP3A4, which are inhibited by CBD.	↑ Cp ↑ adverse effects
Modafinil	Neurotropic drug that is substrate and inhibitor of CYP2C19.	↑ Cp of modafinil and CBD ↓ dose of both drugs should be pondered Monitoring drugs Cp is recommended to define/optimize drug posology individually.
Olanzapine	Antipsychotic drug that is substrate of CYP1A2, which is inhibited by CBD.	↑↓ olanzapine Cp Monitoring olanzapine Cp is strongly recommended to define/optimize drug posology individually
Paroxetine	Antidepressant drug metabolized by CYP2D6, which is inhibited by CBD.	↑ Cp ↑ adverse effects
Sertraline	Antidepressant drug metabolized by CYP2C9, CYP3A4 AND CYP2C19, which are inhibited by CBD. It is also a moderate inhibitor of CYP2C19 and CYP3A4, which metabolize CBD.	↑ Cp of sertraline and CBD ↓ dose of both drugs should be pondered.
Trimipramine	Antidepressant drug metabolized by CYP2C19, which is inhibited by CBD.	↑ Cp ↑ adverse effects ↓ trimipramine dose should be pondered

↑, increase; ↓ decrease; ↑↓, variability (i.e. enhance or decrease) Cp, plasma concentration.

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3. Discussion

Despite all the data already available, the key idea remains associated to a personalized therapy which should be follow-up with care about the possible interactions but also to assure that the therapeutic doses are in the expected plasmatic dose.

Among the possible side effects, the data collect in EudraVigilance – European database of suspected adverse drug reactions reports (https://www.adrreports.eu/en/index.html; https://dap.ema.europa.eu/analytics/saw.dll?PortalPages; assessed December 30th, 2023) for the drugs already approved and prescribed with these compounds are still scarce. Certainly, their lower prescription contributes to a better control, especially because stabilizing the pathologies that benefit of this associations are challenging and the follow-up of the patients is done in very careful way.

Up today, various institutions are aware of these drug interactions and present data and alerts in their websites to prevent them. In a very resumed way, for instance, the Cannabinoid (PRECIPITANT) Medication Affecting the Metabolism of Another (OBJECT) Medication, proved by the Pennsylvania State University, College of Medicine, Dept of Pharmacology (Hershey, PA) it is a good example (https://sites.psu.edu/cannabinoid; assessed January 30th, 2024).

In a near future, the personalized genetic sensibility for the intake of cannabinoids should be always a start point for the therapeutic. Future research directions may also be highlighted. For instance, from the feedback in clinical practice in palliative care, patients doing cannabinoids with opioids, in a first moment a decrease of the daily dose of the last is recommended but after a few days they need to come back to higher levels to get a better improvement in pain relief. This kind of situations need clinical trials that could also be observational but that would allow a better understanding of the doses to be prescribed to patients in a more real clinical evidence, which complete the data provided by the clinical trials.

4. Materials and Methods

Detailed evaluation of potential interactions in adjuvant therapy with cannabinoids were provided for the selected pathologies where cannabinoids have been approved, and/or can be used off the label in benefit for patients. Selected chronic diseases include Epilepsy, ASD, Oncology, Multiple Sclerosis and Chronic Pain were also checked.

A non-systematic literature searches it was performed on PubMed (MEDLINE), Medscape and clinicaltrials databases (no date limitations due to scarce information in some of the possibilities). The searching terms were “cannabinoid” AND “drug interaction” OR “anticonvulsivant” OR “antiseizure” OR “analgesic” OR “oncology” OR “chronic pain” OR “Autism” OR “multiple sclerosis”. Exclusion criteria included: articles written in Chinese or German; articles in which no drug interactions were investigated; and articles with only in vitro/in silico evidence.

The authors screened all retrieved papers and included all original studies written in English, published as full papers or abstracts, and met the selection criteria. The se-lection criteria included studies with participants diagnosed with ASD treated with C. sativa L extracts. or isolated cannabinoids, such as CBD, CBDV, THC, etc., with or without a comparison group. Due, again, to scarce data and since the reported outcomes were expected to vary, no specific outcomes were defined to facilitate a comprehensive evaluation of the available studies in this area. All potentially eligible studies were considered regardless of study design. At initial screening, the studies were assessed independently for potential inclusion by title and abstract. Following the initial screening, the full text of eligible publications was examined, and a final decision for inclusion was made. In addition, citations in the selected articles were reviewed by authors for identifying supplementary eligible articles. The authors extracted information about studies design, characteristics of participants, characteristics of the treatment, and observed outcomes and adverse effects. It was collected also reported data regarding ongoing studies, as retrieved in ClinicalTrials.gov. The

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results of the study were presented in a narrative summary and summarized in tables organized around the characteristics of the studies.

Scoping reviews are a relatively new approach of evidence synthesis that are growingly used in biomedical research fields and, perhaps at lesser extent, in other various re-search disciplines, albeit still lacking full universal consents about their definition, practical methodologies and use circumstances. Details are specified in our recent previous work [43]. Briefly, this type of reviews aims primarily to figure out and map the extent (depth and breadth) of scientific evidence on a particular topic, field, concept, or issue, unveil potential knowledge gaps, possibly clarify key concepts and thus inform both research conduct and practical decision- and policy-making. Scoping reviews are distinguished from other reviews, such as systematic reviews, by an extended breadth of includible literature, a more systematic and comprehensive selection of available scientific literature, and a greater flexibility in drawing conclusions and receiving scientific community criticism to further advance research in the tackled topic, approaching broadly diversified topics that also impose an analysis of a wide range of data and topics [43].

Being permitted to rely on all stages of pharmaceutical, medical, and biomedical research including experimental, preclinical, translational, clinical, and real-world evidence phases, a scoping review was then preferable from our point of view. This is mainly due to the fact that published works on these compounds are characterized by a very rapid expansion, especially in the very recent years. For instance, a search on PubMed with “THC Drug interaction”, and other “CBD Drug interaction”, as a keyword returns more than 1175 and 485 results publications throughout 2023~1973 respectively (for CBD only after 1975 publications were found). The same keywords return 262 and 297 results strikingly dated in the last five years, respectively. A similar tendency it was verified in the other databases consulted.

5. Conclusions

Despite the fact that nowadays there is more and more research in this area, there are still many gaps. Data provide to health professionals should be translational from the research validating the necessary evidence to use cannabinoids with greater security. Medication reconciliation (formal process of the most accurate medications for a patient) implies also the evaluation of the potential drug-drug interactions. The prescription medications can have drug-drug interactions among them, with the cannabinoids, but also with simultaneous intake of herbal medications, over the counter medications, supplements. All of them contribute to change the outcomes of the therapeutic due to the impact on their pharmacodynamic and pharmacokinetic. All the data in this review provides, for the first time, clear indications for the chronic diseases validated treatments with cannabinoid-based drugs and will be helpful to enhance patient safety. Nevertheless, the pharmacovigilance, the notifications of the side effects and/or abnormal events, the real-world collect information, should be provide to a better understanding of the process which allow to improve all the recommendations.

It is clear that clinical data is scarce and need a robust information which allow doctors to deal with safe and more accurate prescription of cannabinoids.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, Maria G Campos and Ana Fortuna; methodology, Maria G Campos and Ana Fortuna; validation, Maria G Campos and Ana Fortuna; investigation, Maria G Campos and Ana Fortuna; resources, Maria G Campos and Ana Fortuna; writing—original draft preparation Maria G. Campos, Maria China, Mariana Claudio, Miguel Capinha, Rita Torres, Simão Oliveira, and Ana Fortuna; writing—review and editing, Maria G Campos and Ana Fortuna; supervision, Maria G Campos and Ana Fortuna; project administration, Maria G Campos and Ana Fortuna; All authors have read and agreed to the published version of the manuscript.” Authorship must be limited to those who have contributed substantially to the work reported.

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