PHARMACOKINETICS OF ORAL TETRAHYDROCANNABINOL AND CANNABIDIOL IN HUMANS: A SYSTEMATIC CRITICAL REVIEW

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Running heading: Pharmacokinetics of oral cannabis-based medicines

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ABSTRACT

Background. The therapeutic potential of cannabis has aroused a growing interest among health professionals. Currently, medicines and phytotherapeutics containing cannabis derivatives such as tetrahydrocannabinol (THC) and cannabidiol (CBD) are marketed; however, the pharmacokinetic data of these products are scant.

Objective. The aim of this review was to systematically collect the data published in this area.

Methods. A systematic review of the literature was carried out in the PUBMED / MEDLINE, Current Contents, LILACS, Scielo databases, in search of all the articles that included THC and CBD pharmacokinetic data in humans, administered orally with exact doses.

Results. After applying inclusion criteria, 14 studies were found. In general, it is described that absorption increases in the company of high-fat foods, repeated doses prolonged the half-life, the products have extensive body distribution, and liver damage increased the maximum concentration reached by derivatives, forcing reduction in the dose. Kidney failure does not significantly influence the pharmacokinetics of CBD. The maximum doses used were 35 mg of THC and up to 6000 mg of CBD. No serious adverse events were reported. However, due to the differences between formulations in the net content of the derivatives, the purity of the products and the heterogeneity of the population, it is not possible to generalize the pharmacokinetic parameters of these studies.

Conclusion. More and better studies are required to establish a safer and more effective dosage for each medicinal cannabis formulation.

Keywords: Medical Marijuana, cannabis, cannabinoids, cannabidiol, pharmacology, pharmacokinetics.

PROSPERO registration number: CRD42019125831

Key Points:
- Knowledge about the temporal course of the concentrations and quantities in the body of cannabis derivatives and metabolites is needed for a safe prescription of cannabinoids.

- More studies with greater power in their methodological design are required in order to make recommendations for population use of medicinal cannabis.

1. INTRODUCTION

Products derived from the Cannabis sativa plant have been used for thousands of years in traditional medicine, religious ceremonies and as a psychoactive substance. This plant belongs to the class of dicotyledonous, fourth order (urtical) and Cannabinaceae family. In general, recognize three subspecies: sativa, indica and ruderalis, which are distinguished by the anatomy of the plant, the growth habit and the variation of the leaves and the types of seeds[1].
The plant contains more than 600 compounds, includes approximately 100 cannabinoids and 200 terpenes, flavinoids and alkaloids[2]. **Figure 1.**

The endocannabinoid system is a complex signaling network that includes endogenous cannabinoid ligands (anandamide and 2-arachidonoyl glycerol), enzymes (fatty acid amide hydrolase and monoacylglycerol lipase) and cannabinoid receptors coupled to protein G, CB1 and CB2[3]. CB1 receptors are found mainly in the central nervous system (hippocampus, cortex, cerebellum, basal ganglia) and, to a lesser extent, in the peripheral nervous system, adipocytes, liver, pancreas and skeletal muscle[4]. CB2 receptors are expressed primarily in lymphatic tissue, gastrointestinal tract and peripheral nervous system, but have also been identified in the central nervous system, for example, in the dorsal nuclei of the vagus nerve, the spinal nucleus of the trigeminal and the microglia[5, 6]. Δ9-THC is a partial agonist of the CB1 and CB2 receptors and exerts its psychoactive effects and the transmission and modulation of pain through CB1 agonism. On the contrary, CBD acts as a functional antagonist of CB1 receptors, which is why it is attributed antipsychotic and neuroprotective effects, in addition to counteracting the acute psychotropic effects of cannabis intake[7, 8] Thus,

the endonannabinoid system modifies various physiological processes such as balance control, appetite stimulation, blood pressure, pain relief, nausea and vomiting, memory, learning and immune response.[9-11]

All these properties have aroused a growing interest among healthcare professionals and general public for their therapeutic potential, which has led to the development of a variety of non-standardized products derived from the plant and the production of other synthetic cannabinoids[8] Some countries, such as the United States, have approved an oral solution of pure CBD (Epidiolex), for refractory epileptic syndromes control, like Lennox-Gastaut and Dravet syndromes[12] It also is being studied for other indications such as Crohn's disease, Alzheimer dementia, Parkinson's disease, social anxiety, among others[13]. Drugs based on CBD and Δ^9-THC (Nabiximol) have been approved in countries such as Colombia, Chile, Mexico, Australia, Germany, Italy, Denmark, Finland, United Kingdom, Poland, Spain, Sweden, Switzerland, Canada and Israel, as a treatment of moderate to severe and refractory spasticity secondary to multiple sclerosis[14]. However, other products derived from the Cannabis have also been produced that do not have medical quality control or standardization, so the concentrations of each compound can be variable and even unknown[15-17], which can lead to adverse reactions.

While the effects of phytocannabinoids are known, there is little information on their pharmacokinetics (PK) and pharmacodynamics. PK parameters are essential to create solid, standardized and safe formulations, which can be used in efficacy studies or to make an adequate dose adjustment according to interindividual variations and specific medical conditions. These parameters are what allow an optimal prescription and the minimization of adverse effects[13]. In a systematic review published in 2018[18], 25 publications were found to report PK parameters after administering Δ^9-THC / CBD and only 9 studies CBD exclusively. Only one study reported CBD bioavailability in humans, which was 31% after smoking[19], and a study with children was included[20]. Route of administration varies from intravenous in 1 study, aerosol, oral capsules or drops, to vaporization and cigarettes in 8 studies. A limitation of this review is, precisely, that multiple routes of administration were accepted as well as data from animal studies and without considering physiological characteristics such as age, body mass index and comorbidities, that interfere with PK and would prevent extrapolating the findings to real population. Additionally, this review did not include recent phase I studies with ascending and multiple doses of CBD[21], as well as analysis of patients with varying degrees of hepatic impairment[22]. Therefore, there are no accurately defined dosage recommendations, as such, a more focused review is needed. Moreover, this review only includes oral formulations, as these are expected to be most common route of administration of cannabis-based medications, and takes into account healthy volunteers and ill patients. This was done in the search for a lower data extrapolation error and to potentially lead to dose calculation fort he general population. The aim of this systematic review is to synthetize available data on PK parameters of orally administered Δ^9-THC and CBD in healthy or ill population.

METHODS

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Protocol is available in The International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42019125831).

2.1. Eligibility criteria

Selected studies met the following criteria: cross-sectional studies and clinical trials including human beings of any age, healthy or sick, in which Δ^9-THC or CBD had been administered orally, alone or in combination of both, with defined doses, that report plasma concentrations over time, which allows the calculation of, at least two of the following PK parameters: absorption, maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC), half-life ($t_{½}$), total body clearance (CL), elimination rate constant (K_e) peak urinary concentrations (U_{max}) of metabolites or volume of distribution (V_d). Studies on synthetic cannabinoids or additional molecules, with routes of administration other than oral, or where Δ^9-THC or CBD were used as food or for recreational purposes were excluded"

2.2. Search

Published and unpublished studies were included, **in Spanish and English and with no time limit**. The search was carried out in Pubmed/Medline, Current Contents, LILACS and Scielo databases. The following terms were used as a search strategy: Medical marijuana, cannabis sativa, cannabis indica, cannabinoids, cannabis,

Pharmacology, Pharmacokinetics, Pharmacodinamics, Kinetics. **Supplemental Table S1** presents the complete search strategy. Other information resources such as textbooks, brochures, references of articles and exchange with specialists working on the subject were reviewed. **No restriction was made by language**. The search was carried out the week of august 8, 2019 and was updated in the week of April 27, 2020. Publication bias, derived from the selective publication of results, was not formally assessed, although it is not suspected due to the wide inclusion of information sources.

2.3. Studies selection and data extraction

For the selection of the studies, two researchers evaluated the results obtained in the searches. Duplicates were excluded. Title and abstract of each reference were then inspected to assess eligibility criteria. Subsequently, full texts were reviewed for final inclusion. Kappa coefficient (κ) for agreement between the two researchers was calculated. Articles included were analyzed and the following data were extracted in a Microsoft Excel template: type of population, sample size, product ingested, dose and reported PK data.

2.4. Quality assessment

Each study was evaluated by means of a 11-items tool specifically created for the review (**Supplemental Table S2**) based on The ClinPK Statement[23], the Tool for Before-After (Pre-Post) Studies With No Control Group from the National Heart Lung and Blood Institute[24], and recommendations for optimal sample size[25], number of measurements[26], and analytical methods[27] in PK models. This tool sought to detect possible limitations in the sample size, the way phytocannabinoids were administered or in metabolite measurement or PK parameters calculation. This tool was developed since there is not a validated method for risk of bias of this type of design. It was applied by two investigators with training in pharmacology and disagreements were resolved by a third investigator. Finally, quality assessment was calculated.

2.5. Synthesis

The synthesis of the data was carried out in a narrative manner specifying the models obtained and the parameters calculated. Adverse effects were also recorded.

3. RESULTS

3.1. Search and studies selection

Exploration of databases provided a total of 1260 citations. Of these, duplicate records [34] and those that did not fulfill eligibility criteria (1181) were discarded. After this initial exclusion, 45 full text articles were reviewed, and 14 studies were finally included. There were no references from other information resources **Figure 2**. Agreement in the selection was good (κ=0.79; 95%CI: 0.68 to 0.89).

3.2. Characteristics of studies

Table 1 summarizes the main characteristics of the fourteen studies analyzed. In total, 173 men and 160 women were involved, with an average of 24 subjects per study ranging from 1 to 84 years old. In seven of the fourteen studies (50%), the subjects were fasting. In seven of the fourteen articles (50%), healthy volunteers were employed. The other studies included patients with varying degrees of hepatic impairment[22], renal impairment[28], pancreatitis and abdominal pain[29], elderly people and Alzheimer's dementia[30, 31] and 3 with refractory epilepsy[32-34]

The analyzed studies include 4 products: (i) natural extracts[33, 35], (ii) 99.9% of purified CBD[32, 36, 37], (iii) epidiolex[21, 22, 28, 34, 38], (iv) namisol[29-31, 39]. The maximum doses used were 35 mg of THC and up to 6000 mg of CBD (17 subjects between 750 mg and 6000 mg[21] and 12 subjects with 750 mg[38]). A single dose was used in twelve of the fourteen articles (86%).

In all studies, C_{max}, T_{max} and AUC were extracted along with some additionally reported PK parameters. In general, the studies did not make an explicit calculation of the sample size or any consideration about its statistical power. It was not specified how the doses they used were calculated or from where they were extrapolated and in some studies body composition or sex differences were not considered, that could lead to changes in the pharmacokinetics of the subjects. The quality assessment is presented in **Supplemental Figure S1** and the detailed description of each item in **Supplemental Table S3**. The agreement in this assessment was high (κ = 0,94 95% CI 0,89 to 0,99).

3.3. PK parameters

Table 1 and **2** summarizes the PK parameters obtained in the studies evaluated. The average Tmax was 3.06 h (1-5) for CBD and 1.17 h (1-2) for THC; while the average plasma elimination half-life for CBD was 19.1 h and for THC it was 2.55 h. **Figure 3** indicates that there is a linear relationship between the dose used and the Cmax (panel a and b) or the AUC (panel c and d) of CBD and THC reached after a single dose with commercial products (not including the study with natural extracts).

Eichler et al.[35] evaluated the differences between the extracts subjected to heating (140 ° C for 12 min) and those not subjected of THC + CBD, finding that the AUC for THC was 2.81 times greater (1.09, vs. 3.07 ng / ml * h, see **Table 2**) when a natural extract was not heated. This finding is contradictory since the relative bioavailability of the heated extract is greater (83%). For CBD, Manini et al.[36] found that the absorption of CBD increased 4.85 times in the fed state. De Vries[29] shows in patients with chronic pancreatitis, that absorption was late and presented greater variability compared to healthy volunteers.

Klumpers et al[39] reported that THC clearance had a variability of 28% but it is higher for 11-OH-THC accounting up to 70%. For Manini et al.[36] urinary excretion of CBD was reported unchanged in less than 5% total and urinary concentrations of conjugates after a dose of 400 mg of CBD, occurred at 6 hours and at doses of 800 mg of CBD at 4 o'clock.

CBD has phase 1 hepatic metabolism by CYP 2C19 and 3A4 enzymes resulting in the metabolites 7-carboxy-CBD, (most important active metabolite), 7-hydroxy-CBD and 6-hydroxy-CBD and phase 2 metabolism by 5'-diphosphoglucuronosyltransferase (UGT) isoforms 1A7, 1A9 and 2B7[40].
According to the findings of Taylor et al.[21], the main circulating metabolite of CBD is 7-carboxy-CBD (half-life 25 to 30 h), followed by 7-hydroxy-CBD (half-life 14 to 19 h) and to a lesser extent 6-hydroxy -CBD half-life 23 to 41 h). After administering multiple doses, it was shown that Cmax increased 1.6 times and AUC 1.9 times on day 7, while plasma concentrations decreased from that day in a multiphasic manner, with a half-life of 56 and 61 hours for 750 mg and 1500 mg respectively . In a second study, Taylor et al. [22] found that Cmax varies according to the severity of hepatic impairment, resulting in 233, 354 and 381 ng / mL for mild, moderate and severe insufficiency respectively, versus 148 ng / mL for subjects with normal liver function. The apparent clearance of CBD was reduced in all hepatic impairment groups in relation to subjects with normal liver function (normal liver function: 422.23 L / h; mild, modera te and severe liver failure: 285.93, 172.01 and 82.02 L /). Tayo et al. [28]were the first to investigate the pharmacokinetics of CBD in subjects with renal impairment, no statistically affected differences were observed in Cmax, AUCt, AUC ∞ or Tmax values compared to subjects with normal kidney function.

3.4. Adverse effects

Consistently reported events include: drowsiness (which seems to increase when co-administered with clobazam); dizziness; impaired coordination; headache; paraesthesia; heat sensation; conjunctival injection; visual disturbances; abdominal discomfort; dry mouth; tremor; paleness; and moderate anxiety of short duration. No higher prevalence of adverse events was observed in patients with liver disease, renal impairment or in co-administration with fentanyl. Only one patient discontinued treatment due to these reactions and no serious adverse events occurred in the analyzed studies. There were no clinically significant laboratory findings, blood pressure or heart rate variations, electrocardiographic or physical examination abnormalities. Regarding the psychotropic effects, the administration of CBD was not found to affect learning, memory, psychomotor control and attention, as described with the administration of THC[32]

4. DISCUSSION

This review aimed to systematically compile the available pharmacokinetic data of products containing THC and CBD. Administered orally at different doses and in healthy volunteers and with some diseases; finding, as expected, a high heterogeneity that we grouped in the aspects related to the product, the formulation and the subject.

Regarding the variables dependent on the product, the studies found show a more high heterogeneity with a more variable PK for the extracts, limiting the extrapolation of their results to other products, findings that

correlate with that described by Wang et al.[33] who reported in pediatric population a variability with THC extracts.

Of the formulation-dependent variables, one study found that CBD absorption increased when administered with high-fat foods[37] results also described by Crockett et al.[38] and who also noted a considerable increase in the Tmax of 7-carboxy-cannabidiol when it was administered with alcohol (14h vs 4 hours on an empty stomach); and for THC, in the study of patients with pancreatitis, it was evidenced that absorption decreased due to fat malabsorption that generates a lower bioavailability of the lipophilic compounds THC and CBD, which could also explain this variability[37]. So it is worth thinking about lipid formulations to improve said absorption since this seems to lead to a longer gastric transit time, improving its modification and increasing bioavailability[32].

Likewise, Wheless et al.[34] about the pharmacokinetics of CBD in the pediatric population with refractory epilepsy, showed that steady-state concentrations were reached after 2 to 6 days of treatment and increased in a dose-dependent manner. Additionally, it was shown that the co-administration of clobazam was associated with an increase in exposure to CBD, which implies that constant monitoring of blood levels must be carried out.

Of the dependent variables of the subjects, Tayo et al.[28] did not observe significant changes in the pharmacokinetic parameters in subjects with varying degrees of renal impairment who received CBD compared to subjects with normal renal function; while Taylor et al[22] found CBD clearance decreased in all hepatic impairment groups, which would require close monitoring of the dose. Additionally, Wolowich et al[41] suggested that in addition to the pharmaceutical factor, CYP2C9 polymorphisms could be responsible for the variability and should be considered in the design of future studies.

The clinical importance of the findings of this review lies in tolerability and safety with high doses of CBD and the absence of serious adverse events, both in adults and in the pediatric population.
Additionally, it confirms the inter-individual pharmacokinetic variability of cannabinoids and allows us to suggest that there is a linear relationship between the dose used and AUC of CBD and THC, and that there AUC is the most important parameter thinking about establishing doses in the future, taking into account the characteristics of the product and the formulation in relation to the dose and the characteristics of each patient such as their body composition and comorbidities that may alter the pharmacokinetic processes.

As limitations of this review, it should be noted that, due to the absence of tools for evaluating the quality of pharmacokinetic studies, we developed our own evaluation scale, the quality has not yet been validated and requires additional analysis. Moreover, as there is no a sample size calculation validated for pharmacokinetic studies, then the impact on conclusion related to their quality can be objected and our results could be considered as merely an exploratory analysis.

Conclusion.

The pharmacokinetics and pharmacodynamics of medicinal cannabis products depend on the product, the formulation and the subject to whom it will be administered. The reviewed studies showed that absorption is modified by disease conditions such as pancreatitis, body composition, and food. Regarding its elimination, it can be altered in patients with moderate hepatic impairment, which requires dose adjustment. In general, high doses especially for CBD were well tolerated, with no serious adverse events in both adults, the pediatric population, and patients with renal impairment. More studies with larger sample sizes are required to increase statistical power and make recommendations for population use of medicinal cannabis.

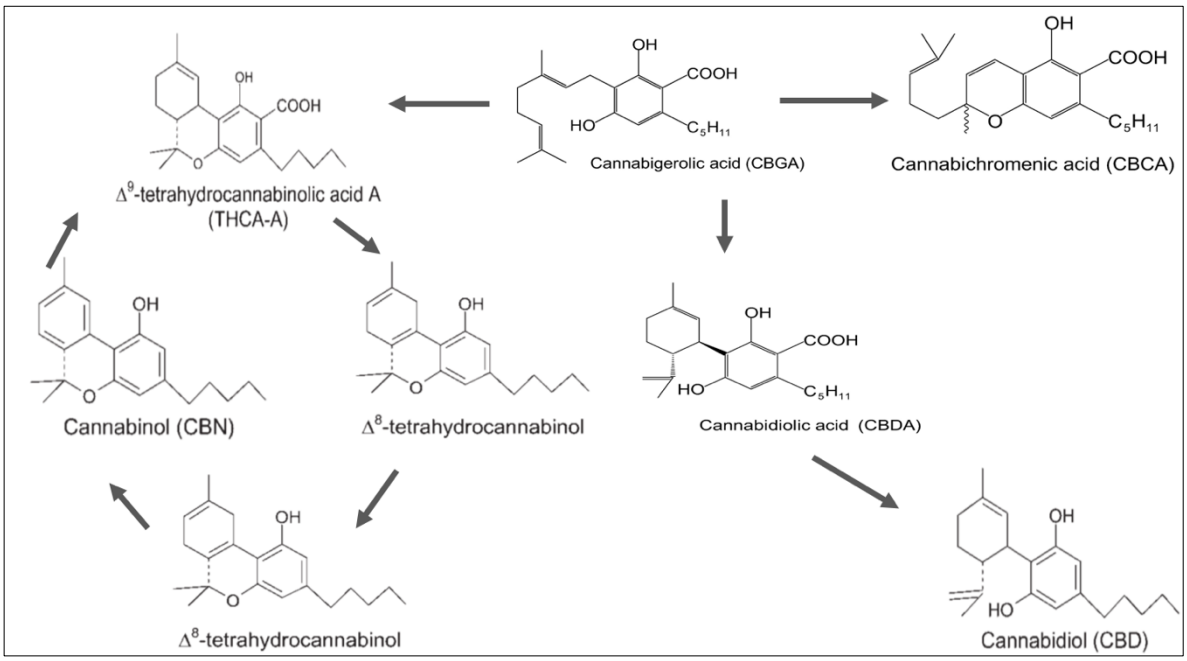


Figure 1. The synthesis of cannabinoids. Modified from Degenhardt FS, F Kayser, O. The Biosynthesis of Cannabinoids. In: Preedy VR, editor. Handbook of Cannabis and Related Pathologies. United Kingdom: Elservier; 2017.

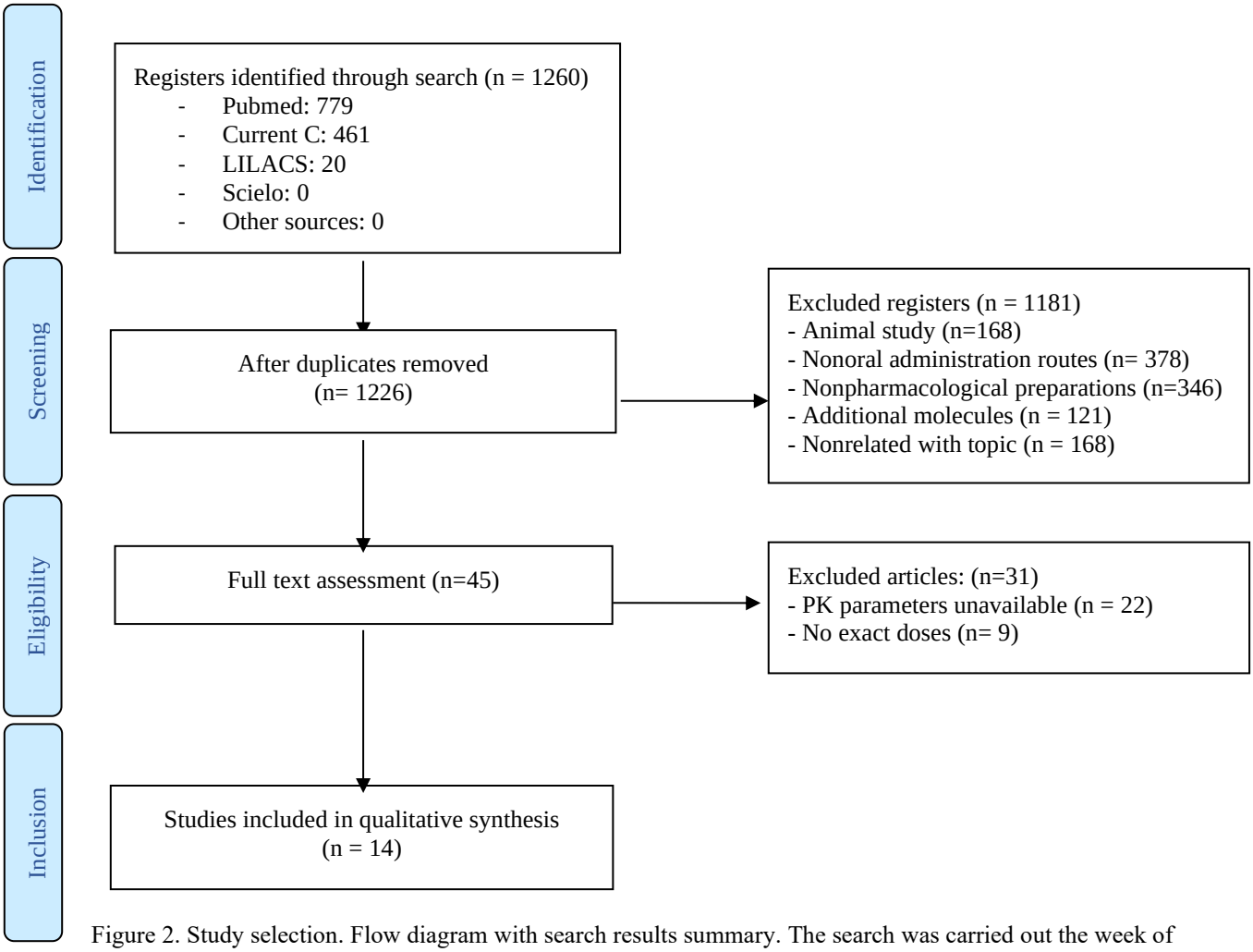


Figure 2. Study selection. Flow diagram with search results summary. The search was carried out the week of august 8, 2019 and was updated in the week of April 27, 2020 Selection of studies has good agreement (κ=0,79; IC95% 0.68 a 0.89).

Table 1. Characteristics of studies reporting CBD PK parameters

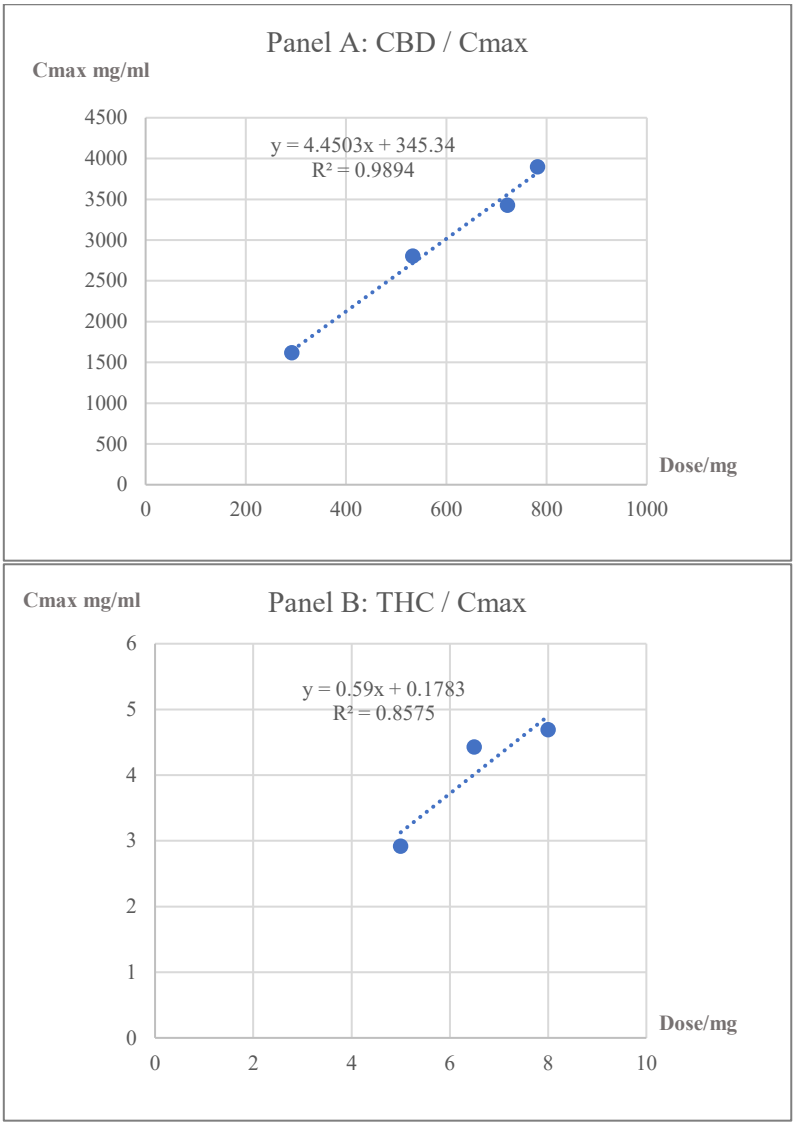
Author	Gender (n)	Clinical condition	Product	Dose (mg)	PK parameters for CBD (mean ± SEM)						
				CBD	Cmax (ng/mL)	Tmax (h)	AUC (ng·h/mL)	t1/2 (h)	CL/F (L/h)	F (%)	Vd/F (L)
Taylor [21]	Men (17) Women 39)	Healthy volunteers	Epidiolex	1500	292 (87.9)	4	1618 (74.6)	14,4	1111 (67)	-	20963 (55)
			Epidiolex	3000	533 (35.1)	5	2802 (35.5)	14,4	1121 (31)	-	23357 (33)
			Epidiolex	4500	722 (52.3)	5	3426 (48.3)	16,6	1445 (53)	-	36575 (67)
			Epidiolex	6000	782 (83.0)	5	3900 (79.3)	15,4	1909 (77)	-	42849 (76)
		Multiple (bid)	Epidiolex	750	732 (39.4)	3	2683 (33.4)	56,4	-	-	-
		Multiple (bid)	Epidiolex	1500	1385 (52.4)	5	9819 (32.3)	60,5	-	-	-
		Fed	Epidiolex	1500	1628 (51.4)	3	8669 (33.9)	24,4	182 (34.2)	-	6349 (1.6)
Taylor [22]	Men (16) Women (14)	Mild	Epidiolex	200	233 (70.5)	3	699 (44.2)	15,7	286 (44.2)	-	5302 (60.1)
	Hepatic impairment	Moderate	Epidiolex	200	354 (42.3)	2	1163 (39.9)	20,5	172 (39.9)	-	4668 (40.1)
		Severe hepatic	Epidiolex	200	381 (52.2)	3	2439 (29.5)	22,1	82 (29.5)	-	2437 (70.5)
		Healthy V.	Epidiolex	200	148 (65.0)	2	434 (73.8)	8,58	422 (73.8)	-	4105 (37.5)
Tayo [28]	Men (16) Women (16)	Mild	Epidiolex	200	200 (42.7)	3	600 (50)	15.5	365 (52.3)	-	6661 (55.5)
	Renal impairment	Moderate	Epidiolex	200	172 (85.3)	2	522 (63.6)	14.6	434 (50.4)	-	7778 (58)
		Severe	Epidiolex	200	155 (40.6)	3	601 (35.9)	13.1	351 (37.3)	-	6016 (39.9
		Healthy V.	Epidiolex	200	153 (74.7)	3	499 (76.6)	11.2	510 (87.6)	-	5800 (29.2)
Eichler [35]	Men (10)	Healthy volunteers	Heated natural extract	27,8	418.2 (0.42)	1	1094.2 (0.84)	-	-	83,3	-
			Unheated natural extract	14,8	1018.8 (0.83)	1	3065.8 (2.95)	-	-	60,4	-
			Dronabinol	-	-	-	-	-	-	100	-
Manini [36]	Men (9) Women (8)	Healthy volunteers + Fentanyl	Placebo	0	0	0	0	0	0	0	0
			CBD 99%	400	181 (39.8)	3	704 (283)	-	-	-	-
			CBD 99%	800	221 (35.6)	3	867 (304)	-	-	-	-
Birnbaum [32]	Men (6) Women (2)	Refractory epilepsy	CBD 99%	100	0.03(0.01)	3	0.53 (0.26)	38.9	1887 (990)	-	1515 (1024)
			CBD 99%	100	0.45(0.3)	2	2.57 (1.6)	24.3	388 (200)	-	194 (100)
Wang [33]	Men (5) Women (4)	Refractory epilepsy Multiple	Natural extract	54.02	1.3	2	-	2	-	-	-
			Natural extract	21,0	1.8	4	-	2	-	-	-
			Natural extract	52,0	2.2	2	-	0.9	-	-	-
			Natural extract	53.3	1.5	2	-	5.1	-	-	-
			Natural extract	23.8	3.6	2	-	3	-	-	-
			Natural extract	25.2	0.8	2	-	5.2	-	-	-
			Natural extract	51.5	1.2	2	-	8.1	-	-	-
			Natural extract	51,0	3.1	1	-	4.5	-	-	-
			Natural extract	23.1	2.5	7	-	5.1	-	-	-
Hobbs [37]	Men (4) Women (6)	Healthy volunteers	CBD 99%	30	2.82	1	476.1	2,53	-	-	32445
			CBD 99%	30	0.65	1.5	98.5	2,29	-	-	63334
Crockett [38]	Men (12) Women (17)	Healthy volunteers	Epidiolex	750	187 (52.2)	4	1190 (48.9)	39.7	630 (48.9)	-	33820 (50.3)
			Epidiolex	750	1050 (56)	3	4870 (46.8)	41.3	154 (46.8)	-	9050 (51.5)
			Epidiolex	750	722 (41.8)	5	3394 (35)	39.4	221 (35)	-	12212 (44.9)
			Epidiolex	750	527 (51.2)	5	2588 (40.6)	36.5	290 (40.6)	-	14966 (24.3)
			Epidiolex	750	354 (59.9)	5	1782 (57.8)	34	421 (57.8)	-	20056 (53.9)
Wheless [34]	Men (33) Women (29) Refractory epilepsy	Grupo 1	Epidiolex	10mg/kg	29.12 - 59.03	3	122 - 173.9	26.4	-	-	-
		Grupo 2	Epidiolex	20 mg/kg	47.19 - 110.5	4	243.6 - 507.1	29.6	-	-	-
		Grupo 3	Epidiolex	40 mg/kg	103.7 - 256.9	3	473.5 - 914.5	19.5	-	-	-

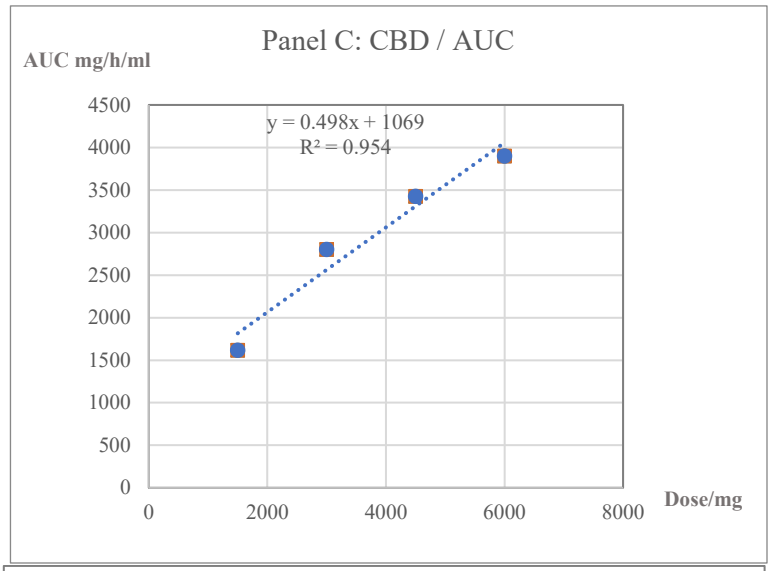
Table 2. Characteristics of studies reporting THC PK parameters.

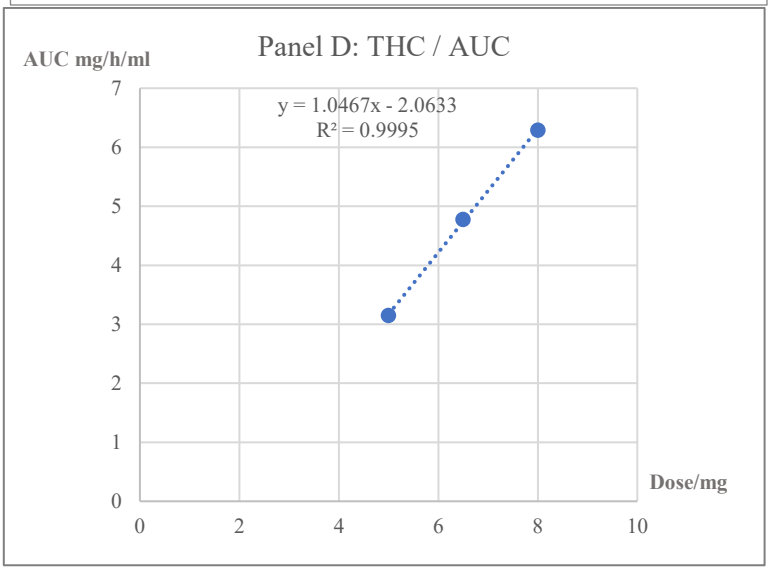
Author	Gender (n)	Clinical condition	Product	Dose (mg)	PK parameters for THC (mean ± SEM)						
				THC	Cmax (ng/mL)	Tmax (h)	AUC (ng·h/mL)	t1/2 (h)	CL/F (L/h)	F (%)	Vd/F (L)
De Vries [29]	Men (15) Women (9) Pancreatitis	Oopioid users	Namisol	8	4.44 (4.4)	2	507.9 (506.7)	1.12	-	-	-
		Non- opioid users	Namisol	8	3.58 (2)	2	447.2 (214.7)	1.10	-	-	-
Ahmed [30]	Men (16) Women (6)	Healthy volunteers	Namisol	1.5	1.42 (0.53)	1	167 (0.80)	-	-	-	-
			Namisol	5	3.15 (1.54)	1	2.61 (0.97)	-	-	-	-
			Namisol	6,5	4.57 (2.11)	1	3.51 (1.26)	-	-	-	-
Ahmed [31]	Men (7) Women (3)	Dementia Multiple (bid)	Namisol	0,75	0.41 (0.56)	1.5	2.21 (2.12)	5.08	0.68 (0.65)	-	-
			Namisol	1,5	1.01 (1.13)	1	4.66 (5.69)	5.06	0.64 (0.78)	-	-
Eichler [35]	Men (10)	Healthy volunteers	Heated natural extract	17,6	4.1 (0.13)	1	1.09 (0.26)	-	-	83,3	-
			Unheated natural extract	10,4	1.02 (0.26)	1	3.07 (0.93)	-	-	60,4	-
			Dronabinol	20	1.02 (0.55)	1	2.65 (1.33)	-	-	100	-
Klumpers [39]	Men (7) Women (7)	Healthy volunteers	Namisol	5	2.30 (1.59)	1	3.93 (0.51)	4.22	26.5 (2.81)	-	889 (200)
			Namisol	5	2.92 (0.41)	1	3.15 (0.35)	1.20	26.5 (2.81)	-	889 (200)
			Namisol	6,5	4.43 (0.62)	1	4.78 (0.97)	1.33	26.5 (2.81)	-	889 (200)
			Namisol	8	4.69 (0.97)	1	6.29 (0.96)	1.31	26.5 (2.81)	-	889 (200)

Abbreviatures: N, number of subjects exposed; THC, tetrahydrocannabinol; C_{max} , maximum measured plasma concentration; T_{max} , time to maximum plasma concentration; PK, pharmacokinetic; AUC, area under the plasma concentration-time curve; $t_{1/2}$,terminal (elimination) half-life; CL/F, oral clearance of drug from plasma; V_d /F, apparent volume of distribution.

Figure 3. Dose/Cmax (Panel A y B); Dose/AUC (Panel C y D); of CBD and THC




Panel C: CBD / AUC
AUC mg/h/ml
y = 0.498x + 1069
R² = 0.954
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
2000
4000
6000
8000
Dose/mg


Panel D: THC / AUC
AUC mg/h/ml
y = 1.0467x - 2.0633
R² = 0.9995
7
6
5
4
3
2
1
0
0
2
4
6
8
10
Dose/mg

References

1. ElSohly M, Radwan M, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. *Progress in the chemistry of organic natural products*. 2017 2017;103doi:10.1007/978-3-319-45541-9_1
2. Degenhardt F, Stehle F, Kayser O. The Biosynthesis of Cannabinoids. In: Preedy V, ed. *Handbook of Cannabis and Related Pathologies*. Elsevier; 2017:13 (9).
3. Buhmann C, Mainka T, Ebersbach G, Gandor F. Evidence for the use of cannabinoids in Parkinson's disease. *Journal of neural transmission (Vienna, Austria : 1996)*. 2019 Jul 2019;126(7)doi:10.1007/s00702-019-02018-8
4. Blanton H, Brelsfoard J, DeTurk N, et al. Cannabinoids: Current and Future Options to Treat Chronic and Chemotherapy-Induced Neuropathic Pain. *Drugs*. 2019 Jun 2019;79(9)doi:10.1007/s40265-019-01132-x
5. Youssef F, Irving A. From cannabis to the endocannabinoid system: refocussing attention on potential clinical benefits. *The West Indian medical journal*. 2012 Jun 2012;61(3)doi:10.7727/wimj.2010.058
6. Mackie K. Cannabinoid receptors: where they are and what they do. *Journal of neuroendocrinology*. 2008 May 2008;20 Suppl 1doi:10.1111/j.1365-2826.2008.01671.x
7. Huestis M. Human cannabinoid pharmacokinetics. *Chemistry & biodiversity*. 2007 Aug 2007;4(8)doi:10.1002/cbdv.200790152
8. Lucas C, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *British journal of clinical pharmacology*. 2018 Nov 2018;84(11)doi:10.1111/bcp.13710
9. Fraguas-Sánchez A, Torres-Suárez A. Medical Use of Cannabinoids. *Drugs*. 2018 Nov 2018;78(16)doi:10.1007/s40265-018-0996-1
10. Brown AJ. Novel cannabinoid receptors. *British journal of pharmacology* 2007 Nov;152,5 567-75. doi:10.1038/sj.bjp.0707481
11. Pisanti S, Malfitano A, Ciaglia E, et al. Cannabidiol: State of the art and new challenges for therapeutic applications. *Pharmacology & therapeutics*. 2017 Jul;175:133-50. doi:10.1016/j.pharmthera.2017.02.041
12. Chen J, Borgelt L, Blackmer A. Cannabidiol: A New Hope for Patients With Dravet or Lennox-Gastaut Syndromes. *The Annals of pharmacotherapy*. 2019 Jun;53(6):603 (11). doi:10.1177/1060028018822124
13. Liu Z, Martin J. Gaps in predicting clinical doses for cannabinoids therapy: Overview of issues for pharmacokinetics and pharmacodynamics modelling. *British journal of clinical pharmacology*. 2018 Nov;84(11):2483 - 24. doi:10.1111/bcp.13635
14. Andrade C. Cannabis and neuropsychiatry, 1: benefits and risks. *The Journal of clinical psychiatry*. 2016 May;77(5):551-4. doi:10.4088/JCP.16f10841
15. Hillen J, Soulsby N, Alderman C, Caughey G. Safety and effectiveness of cannabinoids for the treatment of neuropsychiatric symptoms in dementia: a systematic review. *Therapeutic advances in drug safety*. 2019 May;10:1-23. doi:10.1177/2042098619846993
16. Matheson J, Le-Foll B. Cannabis Legalization and Acute Harm From High Potency Cannabis Products: A Narrative Review and Recommendations for Public Health. *Front Psychiatry*. 2020 Sep;11:591979:1-8. doi:10.3389/fpsyt.2020.591979
17. Jikomes N, Zoorob M. The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular Consumer Products. *Scientific reports*. 2018 Mar;8(1):1-15. doi:10.1038/s41598-018-22755-2
18. Millar S, Stone N, Yates A, O'Sullivan S. A Systematic Review on the Pharmacokinetics of Cannabidiol in Humans. *Frontiers in pharmacology*. 2018 Nov;9:1-13. doi:10.3389/fphar.2018.01365
19. Ohlsson A, Lindgren J, Andersson S, Agurell S, Gillespie H, Hollister L. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. *Biomedical & environmental mass spectrometry*. 1986 Feb;13(2):77-83. doi:10.1002/bms.1200130206

20. Devinsky O, Patel A, Cross J, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. *The New England journal of medicine*. 2018 Mat;378(20):1888-1897. doi:10.1056/NEJMoa1714631
21. Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. *CNS drugs*. 2018 Nov;32(11):1053-1067. doi:10.1007/s40263-018-0578-5
22. Taylor L, Crockett J, Tayo B, Morrison G. A Phase 1, Open-Label, Parallel-Group, Single-Dose Trial of the Pharmacokinetics and Safety of Cannabidiol (CBD) in Subjects With Mild to Severe Hepatic Impairment. *Journal of clinical pharmacology*. 2019 Aug;59(8):1110-1119. doi:10.1002/jcph.1412
23. Kanji S, Hayes M, Ling A, et al. Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement. *Clinical pharmacokinetics*. 2015 Jul;54(7):783-95. doi:10.1007/s40262-015-0236-8
24. National Heart L, and Blood Institute. Study Quality Assessment Tools | NHLBI, NIH. 22 April, 2019. https://www.ncbi.nlm.nih.gov/pubmed/
25. Gueorguieva I, Aarons L, Ogungbenro K, Jorga K, Rodgers T, Rowland M. Optimal design for multivariate response pharmacokinetic models. *Journal of pharmacokinetics and pharmacodynamics*. 2006 Apr;33(2):97-124. doi:10.1007/s10928-006-9009-1
26. Aarons L, Ogungbenro K. Optimal design of pharmacokinetic studies. *Basic & clinical pharmacology & toxicology*. 2010 Mar;106(3):250-5. doi:10.1111/j.1742-7843.2009.00533.x
27. Shah V, Midha K, Dighe S, et al. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. Conference report. *European journal of drug metabolism and pharmacokinetics*. 1991 Dec;16(4):249-55. doi:10.1007/BF03189968
28. Tayo B, Taylor L, Sahebkar F, Morrison G. A Phase I, Open-Label, Parallel-Group, Single-Dose Trial of the Pharmacokinetics, Safety, and Tolerability of Cannabidiol in Subjects with Mild to Severe Renal Impairment. *Clinical pharmacokinetics*. 2020 Jun;59(6):747-755. doi:10.1007/s40262-019-00841-6
29. de Vries M, Van-Rijckevorsel D, Vissers K, Wilder-Smith O, Van-Goor H. Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability. *British journal of clinical pharmacology*. 2016 Mar;81(3):525-37. doi:10.1111/bcp.12811
30. Ahmed A, van-den-Elsen G, Colbers A, et al. Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: a randomized controlled trial. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2014 Sept;24(9):1475-1482. doi:10.1016/j.euroneuro.2014.06.007
31. Ahmed A, van-den-Elsen G, Colbers A, et al. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. *Psychopharmacology*. 2015 Jul;232(14):2587-2595. doi:10.1007/s00213-015-3889-y
32. Birnbaum A, Karanam A, Marino S, et al. Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy. *Epilepsia*. 2019 Aug;60(8):1586-1592. doi:10.1111/epi.16093
33. Wang G, Bourne D, Klawitter J, et al. Disposition of oral delta-9 tetrahydrocannabinol (THC) in children receiving cannabis extracts for epilepsy. *Clinical toxicology (Philadelphia, Pa)*. 2020 Feb;58(2):124-128. doi:10.1080/15563650.2019.1616093
34. Wheless J, Dlugos D, Miller I, et al. Pharmacokinetics and Tolerability of Multiple Doses of Pharmaceutical-Grade Synthetic Cannabidiol in Pediatric Patients with Treatment-Resistant Epilepsy. *CNS drugs*. 2019 Jun;33(6):593-604. doi:10.1007/s40263-019-00624-4
35. Eichler M, Spinedi L, Unfer-Grauwiler S, et al. Heat exposure of Cannabis sativa extracts affects the pharmacokinetic and metabolic profile in healthy male subjects. *Planta medica*. 2012 May;78(7):686-91. doi:10.1055/s-0031-1298334
36. Manini A, Yiannoulos G, Bergamaschi M, et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *Journal of addiction medicine*. 2015 Jun;9(3):204-10. doi:10.1097/ADM.0000000000000118
37. Hobbs J, Vazquez A, Remijan N, et al. Evaluation of pharmacokinetics and acute anti-inflammatory potential of two oral cannabidiol preparations in healthy adults. *Phytotherapy research : PTR*. 2020 Jul;34(7):1696-1703. doi:10.1002/ptr.6651
38. Crockett J, Critchley D, Tayo B, Berwaerts J, Morrison G. A phase 1, randomized, pharmacokinetic trial of the effect of different meal compositions, whole milk, and alcohol on cannabidiol exposure and safety in healthy subjects. *Epilepsia*. 2020 Feb;61(2):267-277. doi:10.1111/epi.16419

39. Klumpers L, Beumer T, van-Hasselt J, et al. Novel Delta(9) -tetrahydrocannabinol formulation Namisol(R) has beneficial pharmacokinetics and promising pharmacodynamic effects. *Br J Clin Pharmacol*. 2011 Dec;74(1):42-53.
40. Huestis M, Solimini R, Pichini S, Pacifici R, Carlier J, Busardò F. Cannabidiol Adverse Effects and Toxicity. *Curr Neuropharmacol*. 2019 Oct;17(10):974-989. doi:10.2174 / 1570159X17666190603171901
41. Wolowich W, Greif R, Kleine-Brueggeney M, Bernhard W, Theiler L. Minimal Physiologically Based Pharmacokinetic Model of Intravenously and Orally Administered Delta-9-Tetrahydrocannabinol in Healthy Volunteers. *European journal of drug metabolism and pharmacokinetics*. 2019 Oct;44(5):691-711. doi:10.1007/s13318-019-00559-7