A marijuana-drug interaction primer: Precipitants, pharmacology, and pharmacokinetics

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ABSTRACT

In the United States, the evolving landscape of state-legal marijuana use for recreational and/or medical purposes has given rise to flourishing markets for marijuana and derivative products. The popularity of these products highlights the relative absence of safety, pharmacokinetic, and drug interaction data for marijuana and its constituents, most notably the cannabinoids. This review articulates current issues surrounding marijuana terminology, taxonomy, and dosing; summarizes cannabinoid pharmacology and pharmacokinetics; and assesses the drug interaction risks associated with co-consuming marijuana with conventional medications. Existing pharmacokinetic data are currently insufficient to fully characterize potential drug interactions precipitated by marijuana constituents. As such, increasing awareness among researchers, clinicians, and federal agencies regarding the need to conduct well-designed in vitro and clinical studies is imperative. Mechanisms that help researchers navigate the legal and regulatory barriers to conducting these studies would promote rigorous evaluation of potential marijuana-drug interactions and inform health care providers and consumers about the possible risks of co-consuming marijuana products with conventional medications.

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Contents

1. Introduction

Marijuana, or cannabis, is the most commonly consumed scheduled or illicit substance worldwide (Degenhardt et al., 2013; Vergara et al., 2017). State restrictions on access to marijuana and derivative products in the United States have been relaxing since 1996, fostering the appearance of state-legal dispensaries and an increasingly diverse market of commercially available products (Jikomes & Zoorob, 2018; Maxwell & Mendelson, 2016; Vergara et al., 2017). Patterns of consumer use are similarly in flux. In 2013, there were an estimated 181.8 million recreational users aged 15 to 64 years (WHO, 2016). By 2016, the percentage of individuals aged 12 years or older who were current marijuana users was higher than that from 2002 to 2015. This increase was due largely to increased consumption by young adults aged 26 years or older, whose use has increased more than that of young adults aged 18 to 25 years.

Given these changes, the absence of definitive data regarding constituent composition, pharmacokinetics, safety, and efficacy of marijuana products is increasingly conspicuous. These gaps in scientific knowledge about marijuana products are compounded by the lack of definitive information regarding the risk of co-consuming marijuana products with conventional drugs (both prescription and over-the-counter). The shifting legal landscape affords an unprecedented opportunity to study the drug interaction liability of marijuana amidst a wealth of information regarding constituents, consumption patterns, and safety data from both prescription and illicit synthetic derivatives.

As with most natural products, evaluating the drug interaction risk of marijuana and constituents (e.g., cannabinoids) is difficult due to the complex phytochemistry of the plant and the abundance of derivative products on the commercial market. However, marijuana is unique among natural products in that its constituent composition has been a subject of forensic examination for decades. Additionally, synthetic cannabinoids have been approved for prescription use by regulatory agencies in multiple countries. To facilitate increasing research on the pharmacokinetics and drug interaction risk of marijuana products, this review summarizes cannabinoid constituents, pharmacology, and pharmacokinetics in humans, as well as probable marijuana-drug interactions precipitated by concomitant consumption of marijuana products with conventional drugs.

2. Marijuana products and consumption

According to United States law, the Schedule I substance *Cannabis sativa (C. sativa)* encompasses all non-fibrous components of any marijuana strain (21 USC 802). Pragmatically, the botanical taxonomy of marijuana is far from standardized. *Cannabis* formally refers to a genus of flowering, dioecious plants from which a variety of psychoactive products are prepared; the term also may be used informally to refer to derivative products (WHO, 2016). Accordingly, both *Cannabis* and cannabis, as well as the common name of the plant (marijuana) are used throughout this review.

Although speciation of *Cannabis* is not well understood, probable taxonomic divisions include *C. sativa, C. indica, C. ruderalis,* and perhaps *C. afghanica;* in United States markets, most strains are varieties of *C. sativa* and *C. indica* (Dufresnes, Jan, Bienert, Goudet, & Fumagalli, 2017; Hillig, 2005; Small, 2015; Welling et al., 2016). In addition, "drug" strains cultivated for medicinal or recreational use tend to exhibit greater genetic variation than fibrous *Cannabis* (hemp) strains, probably because *Cannabis* is dioecious, and female plants are preferentially cultivated for their buds (Dufresnes et al., 2017; ElSohly, Radwan, Gul, Chandra, & Galal, 2017).

Members of the genus *Cannabis* produce resin containing a host of phytocannabinoids, some with pharmacological utility. Primarily produced by epidermal trichomes and resin glands, which intersperse with the flowering buds of *Cannabis,* the bulk of the resin is concentrated in the floral clusters of female plants (de Pasquale, Tumino, & de Pasquale, 1974). Psychoactive and therapeutic effects in humans

are primarily a function of the relative content of two dibenzopyran cannabinoids produced by *Cannabis* varieties: [(−)Δ9-*trans*-(6a*R*, 10a*R*)-tetrahydrocannabinol] (THC), the primary psychoactive constituent, and cannabidiol (CBD), the primary non-psychoactive constituent (Fig. 1A) (Grotenhermen, 2016). THC and CBD are the major cannabinoids in 11*C. sativa* and *C. indica* strains (Fischedick, Hazekamp, Erkelens, Choi, & Verpoorte, 2010). As such, cannabinoid studies in humans have focused largely on THC and CBD, and to some extent on cannabinol (CBN), an aromatized monoterpenoid derivative of THC present in marijuana smoke condensate (ElSohly & ElSohly, 2007). Although there is extreme inter-strain variability in THC:CBD ratios, in general, *C. indica* dominant strains, which are short and wide-leafed, tend to produce more CBD relative to THC; the taller and more narrow-leafed *C. sativa* dominant strains tend to produce more THC relative to CBD (Dufresnes et al., 2017; Hillig & Mahlberg, 2004).

Routes of administration for marijuana and derivative preparations (e.g., wax, oils, and resins) include inhalation (smoking), oral consumption, or topical application. The increasing popularity of vaporizing instruments has produced a market for water-soluble emulsions or solutions of cannabinoids for inhalation. Oral forms (edibles) are often prepared by solubilizing constituents of the whole plant in lipids, incorporating into food products, and cooking to de-carboxylate cannabinoid constituents.

Dosing recommendations for marijuana remain nascent, albeit some states have defined a standard dose of THC per serving of edible product (e.g., 10 mg in Washington, California, and Colorado; 5 mg in Oregon). Precise dosing is complicated by inaccurate labeling, a problem inherent to the natural product market (Ekor, 2014; Raynor, Dickinson, Knapp, Long, & Nicolson, 2011). For example, among marijuana products purchased online, 26% contained less CBD than indicated on the label (Bonn-Miller et al., 2017). Cannabinoid content of marijuana also has increased substantially over the last two decades such that the THC concentration of confiscated marijuana reportedly increased by 103% between 1998 and 2008 (ElSohly et al., 2016; Niesink, Rigter, Koeter, & Brunt, 2015). Recommended medical dosing with whole plant products is to "start low, go slow, and stay low," titrating slowly over approximately two-week increments (MacCallum & Russo, 2018). Prescription cannabinoids in the United States are labeled with low initial doses for twice-daily administration (e.g., 2.5 mg dronabinol, 1 mg nabilone, 2.5 mg CBD) (Valeant Pharmaceuticals International, 2006; Greenwich Biosciences, Inc., 2018; AbbVie, Inc., 2017).

Adverse events reportedly ensuing from medical marijuana consumption appear to pertain primarily to THC content; thus, medical users are advised to consume THC with CBD to attenuate THC-associated anxiety and tachycardia and to limit the total daily dose-equivalent of THC to 30 mg/day or less. Higher doses of CBD likely are safe (MacCallum & Russo, 2018). In general, a joint contains approximately one-half gram of marijuana; however, differences in strain and cannabinoid composition preclude accurate estimation of the dose consumed after smoking one joint.

3. Major constituents

"Cannabinoid" originally referred to numerous structurally related C_{21} hydrocarbon compounds isolated from *C. sativa*; however, after THC was identified in 1964 and subsequently identified as the primary psychoactive constituent in marijuana, the term evolved to encompass compounds with pharmacological effects and target receptors similar to those of THC (Ford, Tai, Fantegrossi, & Prather, 2017; Gaoni & Mechoulam, 1964; Stout & Cimino, 2014). As such, cannabinoids include structurally diverse compounds produced by plants (phytocannabinoids) (Hanus, Meyer, Munoz, Taglialatela-Scafati, & Appendino, 2016), humans (endocannabinoids) (Martin, Mechoulam, & Razdan, 1999), or synthetic chemistry (synthetic cannabinoids) (Di Marzo & Petrocellis, 2006; Ford et al., 2017).
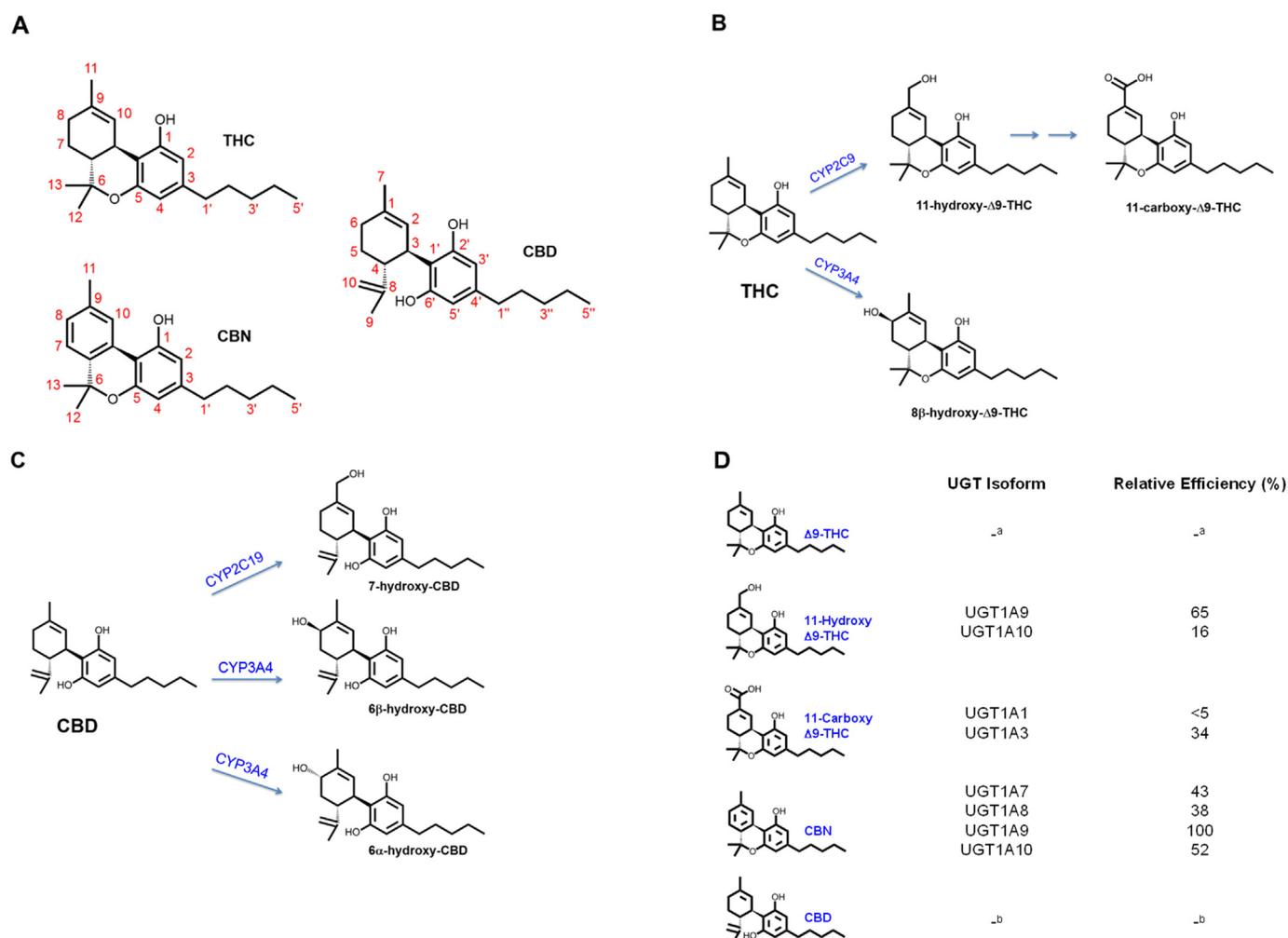
Fig. 1. Structures of THC, CBD, CBN, and their major metabolites. (A) Structures of THC, CBD, and CBN. (B) CYP2C9 catalyzes formation of the primary active THC metabolite, 11-OH-THC, which is subsequently oxidized to the inactive THC-COOH, whereas CYP3A4 catalyzes formation of a second primary, but inactive metabolite, 8β-OH-THC. (C) Primary metabolites of CBD are formed by CYP2C19 (7-OH-CBD) and CYP3A4 (6β-OH-CBD and 6α-OH-CBD). (D) Relative efficiency of glucuronide conjugation of THC and its metabolites, CBN, and CBD by various UGT enzymes, calculated as a percent of UGT1A9 V_{max}/K_m (Mazur et al., 2009). [a] not determined due to lack of UGT activity against THC. [b] not determined due to very low UGT activity toward CBD.

The phytocannabinoids in marijuana compose ten major sub-types (Elsohly & Slade, 2005). However, in total, the marijuana plant probably contains some 500 chemical constituents (ElSohly et al., 2016; ElSohly et al., 2017; Ross & ElSohly, 1995; WHO, 2016). Most of the known *Cannabis* constituents were identified between 1960 and 1990; more recently discovered constituents were isolated from "high potency" strains containing >20% THC by dry weight (Radwan et al., 2015). Different laboratories report varying cannabinoid content in popular commercial strains, with these between-lab differences persisting even after controlling for plausible confounds (Jikomes & Zoorob, 2018).

Synthetic cannabinoids are used as both prescription medications (e.g., dronabinol, nabilone) and drugs of abuse (e.g., "K2", "Spice"). Other synthetic cannabinoids include the HU series (developed at the Hebrew University), the CP series (developed by Pfizer Inc.), and the JWH series (developed by JW Huffman) (Castaneto et al., 2014; Tait, Caldicott, Mountain, Hill, & Lenton, 2016). Initially developed as pharmacological probes of the endogenous cannabinoid system, these synthetic cannabinoids may also be used as drugs of abuse. Synthetic cannabinoids not approved for human consumption have higher affinity for cannabinoid receptors and stronger pharmacologic effects than THC (Tait et al., 2016). As such, adverse effects are considered to be more intense than those observed with THC (Le Boisselier, et al., 2017).

4. Pharmacology

Marijuana has psychotropic effects, including both psychological stimulation and sedation, as well as somatic effects, including analgesia, antinociception, and orexigenia (Grotenhermen, 2003; Kumar, Chambers, & Pertwee, 2001). At high doses, marijuana induces anxiety, tachycardia, and hypertension (Grotenhermen, 2003). Indications for prescription marijuana products include chemotherapy-associated nausea and vomiting (dronabinol and nabilone), AIDS-associated anorexia (dronabinol), and rare epilepsy syndromes (CBD) (Valeant Pharmaceuticals International, 2006; Greenwich Biosciences, Inc., 2018; AbbVie, Inc., 2017). Although cannabinoids have been studied for an extremely wide range of other indications, CBD in particular is increasingly under investigation for indications that benefit from central nervous system cannabinoid receptor activation, including generalized anxiety, obsessive compulsive disorder, panic disorder, and psychosis (Blessing, Steenkamp, Manzanares, & Marmar, 2015; van Amsterdam et al., 2018).

The complex endocannabinoid system underlying these effects, including endocannabinoid production mechanisms, cannabinoid receptors, and cannabinoid-degrading enzymes, is a phylogenetically ancient system that appears to be conserved in all vertebrates (Elphick & Egertova, 2005). The major endocannabinoids in humans are derivatives of arachidonic acid: *N*-arachidonylethanolamine, or

anandamide; 2-arachidonylglycerol; 2-arachidonylglyceryl ether, or noladin ether; and *N*-arachidonyl-dopamine (Di Marzo, 2009; Grotenhermen, 2004; Kendall & Yudowski, 2016; Pertwee & Ross, 2002).

The mechanism of action of phyto-, *endo*-, and synthetic cannabinoids generally involves activation of two G-protein coupled cannabinoid receptors, CB_1 and CB_2, which were cloned in the early 1990s (Kumar et al., 2001; Pertwee, 1997). CB_1 is expressed in both the central and peripheral nervous systems, whereas CB_2 is expressed mainly in the peripheral nervous system, especially in spleen and thymus, and may contribute to the immunomodulatory actions of cannabinoids (Grotenhermen, 2004; Grotenhermen & Muller-Vahl, 2012; Kumar et al., 2001; Schatz, Lee, Condie, Pulaski, & Kaminski, 1997). Activation of cannabinoid receptors inhibits production of adenyl cyclase and may modulate calcium and potassium channels (Grotenhermen, 2004; Kumar et al., 2001; Szabo & Schlicker, 2005) (Fig. 2).

The affinities of phyto- and endocannabinoids for CB_1 and CB_2 have been elucidated using competitive binding assays that measure displacement of the synthetic cannabinoid radioligand, [3H]-CP-55,940, or surrogate measures such as inhibition of cAMP production downstream of cannabinoid receptor activation (Felder et al., 1995; McPartland, Glass, & Pertwee, 2007; Navarro et al., 2018; Showalter, Compton, Martin, & Abood, 1996). Early experiments with CB_1-overexpressing Chinese hamster ovary cell membranes and CB_2-overexpressing mouse pituitary cells showed more potent displacement of [3H]-CP-55,940 by phytocannabinoids compared to endocannabinoids (Felder et al., 1995). For example, THC was a stronger displacer than anandamide at CB_1 by an order of magnitude (K_i, 53 versus >500 nM), and THC and CBN were stronger displacers than anandamide and adrenyl-ethanolamide at CB_2 (K_i, ≤300 versus >2000 nM) (Felder et al., 1995). THC (100 nM) also inhibited forskolin-stimulated cAMP production by ≥50% compared to control in Chinese hamster ovary cells overexpressing CB_1 and CB_2 (Rinaldi-Carmona et al., 1996). A more recent study reported that cannibigerol displaced [3H]-CP-55,940 at concentrations >1000 nM (Navarro et al., 2018). A partial agonist of CB_2, cannabigerol (100 nM) reduced the effect of synthetic CB_1/CB_2 agonists on cAMP production in cells over-expressing both CB_1 and CB_2 (Navarro et al., 2018).

These observations have implications about the mechanism of action of phytocannabinoids. The relatively potent inhibition of
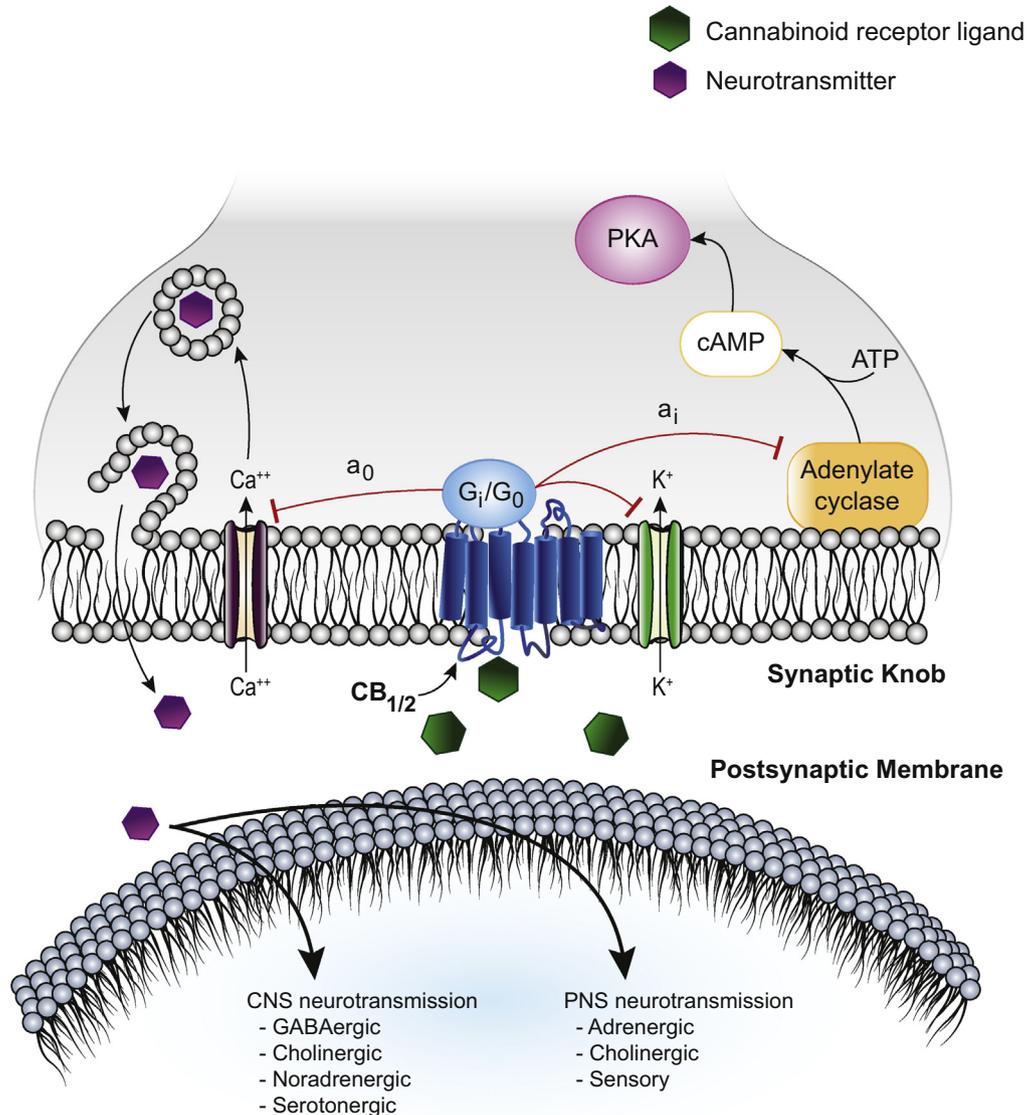
Fig. 2. Effects of cannabinoid ligands on the central nervous system and peripheral nervous system. Activation of the cannabinoid 1 receptor (CB_1) and cannabinoid 2 receptor (CB_2) by cannabinoid ligands inhibits production of adenylate cyclase via activation of a coupled G_i/G_0 G-protein subunit. $CB_{1/2}$ activation also promotes exocytosis of a variety of neurotransmitters, which act broadly on the central and peripheral nervous system (CNS and PNS), perhaps by modulation of calcium and potassium transport.

radioligand binding to CB_1 and CB_2 in these in vitro systems suggests that the phytocannabinoids exhibit higher affinity for human CB_1 and CB_2 compared to some endocannabinoids. Although THC is generally believed to be an agonist of both CB_1 and CB_2, with effects and affinities similar to those of the endocannabinoids anandamide and 2-arachidonoylglycerol, THC has been reported to have pharmacologic effects akin to cannabinoid receptor antagonists. Other investigators have reported THC to be a CB_2 antagonist. These conflicting observations are discussed in detail elsewhere (Pertwee, 2008).

The aforementioned inhibition data indicate preferential binding of cannabinoids to cannabinoid receptors. For example, THC displaced [³H]-CP-55,940 from CB_2 by a greater extent (1.4 times) than from CB_1, and CBN displaced [³H]-CP-55,940 from CB_1 by a greater extent (3.8 times) than from CB_2 (Felder et al., 1995). CBD was reported to bind weakly to CB_1 and CB_2 (K_i, >10 μM and 1.8 μM, respectively), whereas a synthesized enantiomer, (+)-CBD, bound more strongly to CB_1 and CB_2 (K_i, 17 nM and 211 nM, respectively) (Hanus et al., 2005). These data suggest that CBD does not exert its pharmacological effects via cannabinoid receptors (Hanus et al., 2005). More recently, CBD has been proposed to exert its pharmacological effects via binding to 5-HT (serotonin) receptors (Martinez-Pinilla et al., 2017).

5. Pharmacokinetics

The pharmacokinetics of primary phytocannabinoids have been reviewed extensively (Agurell et al., 1986; Grant, Petroff, Isoherranen, Stella, & Burbacher, 2017; Grotenhermen, 2003; Huestis, 2007; Lucas, Galettis, & Schneider, 2018; Stout & Cimino, 2014). The following section summarizes the pharmacokinetic properties of THC and CBD, and to some extent CBN, as they relate to the risk of marijuana-drug interactions.

5.1. Absorption

The rate of cannabinoid absorption into the systemic circulation varies with route of administration. When inhaled (i.e., smoked), systemic absorption of THC, CBD, and CBN is rapid, with maximum plasma concentrations (C_{max}) achieved within 0.02–0.5 h (1.2–30 min) (Table 1 and Supplementary Table 2; note that Table 1 summarizes data from the Supplementary Tables). After oral consumption (i.e., as a prescription drug or in food or oil), the C_{max} of THC, CBD, and CBN is achieved within 1–3.4 h (Supplementary Table 3). Like the rate of absorption, the extent of absorption of cannabinoids into the systemic circulation – as assessed by C_{max} and area under the plasma concentration versus time curve (AUC) – varies substantially with route of administration (Fig. 3, Fig. 4). Compared to oral administration, mean dose-normalized C_{max} for THC, CBD, and CBN was 3–35 times higher, and the AUC for THC was two times higher, after smoking. C_{max} and AUC for THC, CBD, and CBN were similar between oral administration and use of an oral mucosal spray (Table 1).

Assuming linear pharmacokinetics, the estimated absolute bioavailability of THC after inhalation, oral administration, or administration by oral mucosal spray is low (5–7%), suggesting substantial pre-systemic (first-pass) metabolism and/or incomplete absorption into the systemic circulation (Table 1). Incomplete absorption may be the primary driver of the low bioavailability of THC from marijuana smoke, as 23–30% of THC is lost to pyrolysis, and another 40–50% is lost to non-inhaled smoke, leaving 20–37% of the initial THC amount available for pulmonary absorption (Perez-Reyes, 1990). Similarly, the absolute bioavailability of CBD after inhalation is ~30%, whereas that after oral administration (7–13%) or by oral mucosal spray (4%) is much lower (Table 1). These data suggest substantial first-pass metabolism and/or incomplete absorption of CBD after extravascular administration.

Table 1

Dose-normalized C_{max} and AUC of key cannabinoids and metabolites in humans after various routes of administration of cannabinoids.

Cannabinoid	Route of Administration			
	Intravenous	Inhalation	Oral	Oral mucosal
Dose range (mg)				
THC	0.5–5.0	8.9–70	2.5–90	5.4–22
CBD	20	2.0–19	1.5–800	5.0–20
CBN	20	1.6–19	3.3–40	–
C_{max}/Dose (nM/mg)				
THC	130 [90.0–200]	9.9 [7.0–14.1]	1.50 [1.32–1.71]	1.47 [0.63–3.39]
11-OH-THC[a]	4.7 [2.7–8.1]	0.65 [0.40–1.05]	1.10 [0.90–1.34]	1.48 [1.05–2.10]
COOH-THC[a]	23.4 [15.5–35.4]	3.73 [2.31–6.00]	13.3 [9.74–18.0]	22.7–58.1[c]
CBD	109[b]	18.2[b]	0.60 [0.31–1.51]	0.50 [0.20–1.3]
CBN	67.4[b]	20.6[b]	0.58[b]	–
AUC/Dose (min/L)				
THC	1.5 [0.90–2.4]	0.14 [0.10–0.21]	0.07 [0.05–0.10]	0.11 [0.03–0.34]
11-OH-THC[a]	0.15–0.50[c]	0.03 [0.02–0.05]	0.14 [0.12–0.16]	0.16 [0.11–0.22]
COOH-THC[a]	–	0.33 [0.20–0.55]	3.7 [2.2–6.3]	3.4–9.6[c]
CBD	0.83[b]	0.25[b]	0.06-0.11[c]	0.03 [0.02–0.07]
CBN	0.76[b]	0.28[b]	–	–

Values denote geometric means and 95% confidence intervals or range of data presented in the Supplementary Tables. Dashes indicate data were not available.
[a] Normalized to administered dose of THC.
[b] Data from one available study.
[c] Data depict range from two studies.

5.2. Distribution

Cannabinoids sequester in fatty tissues due to their high lipophilicity (logP for THC, CBD, and CBN is 6.97, 5.79, and 4.38, respectively) (Levitt, 2007; Thomas, Compton, & Martin, 1990). Animal studies show the highest accumulation in adipose, liver, and lung tissue (Kreuz & Axelrod, 1973). THC is highly protein bound, primarily to lipoproteins, with a fraction unbound in plasma of <5% (Klausner, Wilcox, & Dingell, 1975). Human blood-to-plasma ratios range from 0.39–0.63 for THC, 0.55–0.59 for the acid metabolite of THC (COOH-THC), and 0.60 for the primary metabolite of THC, 11-OH-THC (Karschner et al., 2012). These data indicate that THC and these metabolites do not partition appreciably into erythrocytes.

5.3. Metabolism

Cytochrome P450 (CYP) 2C9 is the major enzyme that catalyzes the oxidation of THC to the primary metabolite, 11-OH-THC, which is also psychoactive; 11-OH-THC is oxidized further to the inactive COOH-THC (Fig. 1B) (Bland, Haining, Tracy, & Callery, 2005; Bornheim, Lasker, & Raucy, 1992). Compared to healthy human participants homozygous for the *CYP2C9* reference allele (*CYP2C9*1*), participants homozygous for the reduced functional allele (*CYP2C9*3*) showed a three-fold higher median THC plasma AUC when administered a single oral dose of THC (15 mg); the corresponding median COOH-THC AUC was 70% lower in *CYP2C9*3/*3* carriers compared to *CYP2C9*1/*1* carriers (Sachse-Seeboth et al., 2009). CYP3A4 is primarily responsible for catalyzing the oxidation of THC to the second primary but inactive metabolite, 8β-OH-THC (Fig. 1B) (Bornheim et al., 1992; Watanabe, Yamaori, Funahashi, Kimura, & Yamamoto, 2007), which is stereoselectively preferred over 8α-OH-THC. Although other phytocannabinoids and metabolites have other therapeutic effects, such as analgesia, they do not produce appreciable psychoactive effects in humans; thus, THC and 11-OH-THC are generally considered the psychoactive constituents in
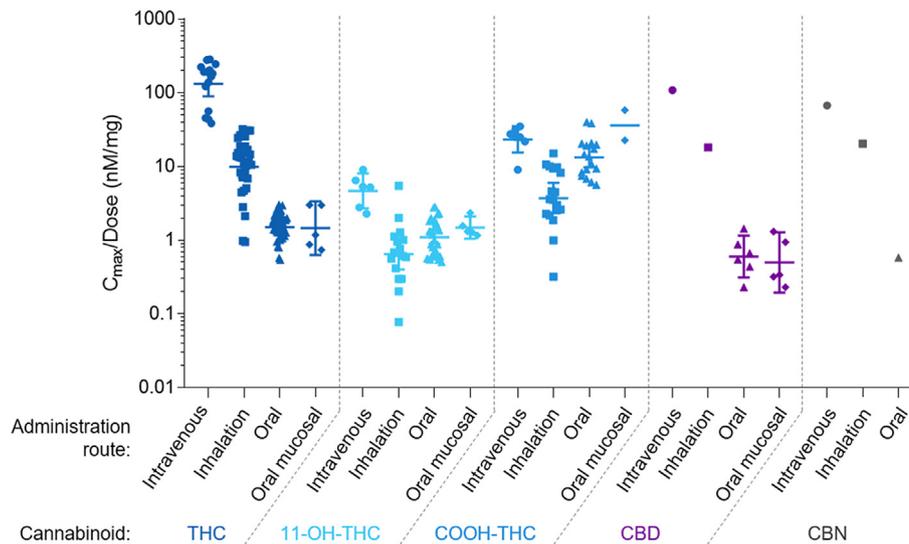
Fig. 3. Effect of route of administration on dose-normalized C_{max} of THC, 11-OH-THC, COOH-THC, CBD, and CBN. Dose-normalized C_{max} after administration of parent cannabinoid (THC, CBD, or CBN). 11-OH-THC and COOH-THC were measured after administration of THC via various routes; metabolite C_{max} was normalized to the administered THC dose. Symbols represent mean values from individual studies (see Supplementary Table). Horizontal and vertical lines represent geometric means and corresponding 95% confidence intervals, respectively. Data were not available for CBN administered via oral mucosal spray.

marijuana (Awasthi, An, Donovan, & Boles Ponto, 2018; Sharma, Murthy, & Bharath, 2012).

CBD is oxidized to form hydroxylated metabolites (Fig. 1C). Side-chain oxidation forms seven other metabolites (Jiang, Yamaori, Takeda, Yamamoto, & Watanabe, 2011). Formation of 7-OH-CBD is catalyzed primarily by CYP2C19 based on metabolite profiling with recombinant enzymes, a high correlation between CBD 7-hydroxylation and (S)-4′-mephenytoin hydroxylation in phenotyped human liver microsomes, and inhibition of this pathway in human liver microsomes by omeprazole (CYP2C19 inhibitor) but not sulfaphenazole (CYP2C9 inhibitor) (Jiang et al., 2011). CYP3A4 generates other minor metabolites, including several with alcohols on the pentyl side chain of CBD (Fig. 1C) (Jiang et al., 2011). One case report showed that CBD is metabolized to >30 urinary metabolites (Harvey & Mechoulam, 1990). Notably, numbering systems are a source of confusion in the marijuana literature, as the metabolically labile allylic sites at C-11 and C-8 in Δ9-THC are

equivalent to C-7 and C-6 in CBD. For example, in older literature, Δ9-THC is sometimes referred to as Δ1-THC (using the monoterpenoid numbering system).

Dose-normalized C_{max} and AUC of the THC metabolites 11-OH-THC and COOH-THC after administration of THC varies with route of administration (Figs. 3, 4 and Table 1). After inhalation, mean dose-normalized C_{max} of THC was higher than that of 11-OH-THC and COOH-THC, whereas the AUC of COOH-THC was higher than that of 11-OH-THC and THC; both the C_{max} and AUC of COOH-THC was higher than those of 11-OH-THC. After administration of THC orally and as an oral mucosal spray, mean dose-normalized C_{max} and AUC of COOH-THC were higher than those of THC and 11-OH-THC (Table 1). These observations may be due to a relatively slower clearance and/or smaller volume of distribution of COOH-THC compared to that of THC and 11-OH-THC.

Of the major phytocannabinoids, only CBN is glucuronidated (Mazur et al., 2009). CBN glucuronidation is catalyzed by the UDP-
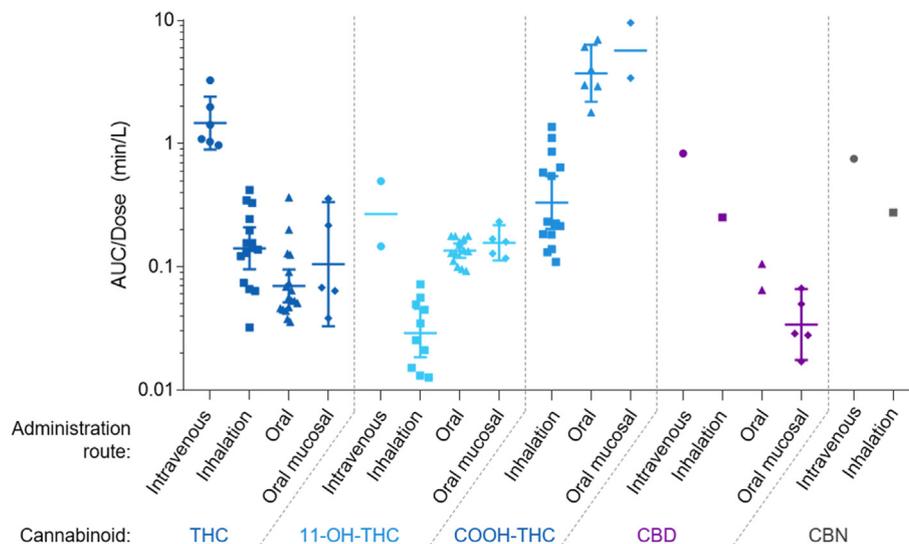
Fig. 4. Effect of route of administration on dose-normalized AUC of THC, 11-OH-THC, COOH-THC, CBD, and CBN. Dose-normalized AUC after administration of parent cannabinoid (THC, CBD, or CBN). 11-OH-THC and COOH-THC were measured after administration of THC via various routes; metabolite AUC was normalized to the administered THC dose. Symbols represent mean values from individual studies (see Supplementary Table). Horizontal and vertical lines trepresent geometric means and corresponding 95% confidence intervals, respectively. Data were not available for COOH-THC following intravenous administration of THC nor for CBN administered orally and via oral mucosal spray.s.

glucuronosyltransferase (UGT) 1A subfamily, with K_m values ranging from 3.4 μM (UGT1A9) to 59 μM (UGT1A10) (Mazur et al., 2009). 11-OH-THC is glucuronidated by UGT1A9 and UGT1A10, with K_m values of 7.3 and 72 μM, respectively. COOH-THC is glucuronidated by UGT1A1 and UGT1A3, with K_m values of 170 and 68 μM, respectively.

5.4. Elimination

Plasma concentration-time profiles for THC and CBD are qualitatively similar and can be described by two- or three-compartment pharmacokinetics (Heuberger et al., 2015; Hunt & Jones, 1980; Wall, Sadler, Brine, Taylor, & Perez-Reyes, 1983). The initial half-life after inhalation ranges from 1.4–12.8 min, whereas the terminal half-life has been estimated at 20–30 h (Heuberger et al., 2015; Ohlsson et al., 1986). Assuming an average weight of 70 kg, mean THC plasma clearance after intravenous administration was 9.9 mL/min/kg and ranged from 2.8–14 mL/min/kg, indicating a low to medium hepatic extraction ratio (Grotenhermen, 2003). Mean THC plasma clearance was reported to be higher in men than in women (14 ± 4.8 vs. 8.1 ± 5.2 mL/min/kg) (Naef, Russmann, Petersen-Felix, & Brenneisen, 2004), suggesting a potential sex-related difference in THC clearance. In other reports, mean plasma clearance of CBD and CBN after intravenous administration to small groups of young men ($n \leq 9$) was comparable to or higher than that of THC (12–20 and 16–22 vs. 11–17 mL/min/kg, respectively), assuming an average weight of 70 kg (Johansson et al., 1987; Ohlsson et al., 1982; Ohlsson et al., 1986). Additional studies involving larger numbers of subjects are needed to confirm these observations.

Urinary excretion of THC and 11-OH-THC persists for up to 3 days after a single dose of THC and for >3 weeks in chronic marijuana smokers (Johansson, Halldin, Agurell, Hollister, & Gillespie, 1989; Leighty, Fentiman Jr., & Foltz, 1976; Lowe et al., 2009; Skopp & Potsch, 2008). Thus, differences in study design produce wide variations in measurements for excretion of THC and metabolites. Although some studies report 20% urinary excretion of THC and metabolites, these results are likely to be time-dependent, as only 0.22% of an 8-mg THC dose was excreted in urine as THC and metabolites during the 0–8 h collection interval after consumption via smoking (Brenneisen, Meyer, Chtioui, Saugy, & Kamber, 2010; Hunt & Jones, 1980; Wall et al., 1983).

THC and CBD, along with their alcohol and acid metabolites, can in principal be converted to their ether and/or acyl glucuronides by conjugation with glucuronic acid; such metabolites have been detected in human plasma and urine (Fig. 1D) (Desrosiers et al., 2014). After intravenous administration of [³H]-labeled THC, 20% of the total radioactive dose was excreted into urine as conjugated metabolites, and 80% was excreted into the feces. Of the THC excreted into the feces, 20% represented unconjugated 11-OH-THC, and 28% represented COOH-THC (Wall et al., 1983). <5% of THC was excreted unchanged in the feces. Unlike THC, a large proportion of CBD was excreted unchanged into the feces after intravenous administration (Ohlsson et al., 1986). The large fraction of 11-OH-THC and CBD excreted into the feces suggests transport of these compounds into the bile by canalicular efflux transporters [e.g., P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and/or multi-drug resistance associated protein 2 (MRP2)].

5.5. Pharmacogenomics

The majority of studies evaluating the pharmacogenomics of cannabinoids have focused on those that modulate the risk of dependency (Hryhorowicz, Walczak, Zakerska-Banaszak, Slomski, & Skrzypczak-Zielinska, 2018). Because cannabinoids are substrates for P-gp (Bonhomme-Faivre, Benyamina, Reynaud, Farinotti, & Abbara, 2008; Brzozowska et al., 2016; Spiro, Wong, Boucher, & Arnold, 2012; Zhu et al., 2006) and BCRP (Brzozowska et al., 2016; Spiro et al., 2012), polymorphisms in either gene that encodes these proteins (*ABCB1* and *ABCG2*, respectively) could influence cannabinoid disposition and the likelihood of marijuana-drug interactions mediated by either

transporter. As described earlier (Section 5.3), among the enzymes that catalyze THC metabolism in humans (primarily CYP2C9, CYP2C19, and CYP3A4), the *CYP2C9*2* and *CYP2C9*3* polymorphisms may lead to reduced formation of 11-OH-THC (Sachse-Seeboth et al., 2009).

6. Drug interactions

6.1. In vitro and animal studies

6.1.1. Interactions with cytochrome P450s

Cannabinoids exhibit multifaceted interactions with the CYPs (Alsherbiny & Li, 2018). For example, THC induced human CYP1A1 mRNA expression in a murine hepatoma cell line (Hepa-1) expressing an inducible CYP1A1 gene, possibly via interactions with the aryl hydrocarbon receptor (Roth et al., 2001). However, THC inhibited CYP1A/1B1 activity (7-ethoxyresorufin O-deethylation) in human liver microsomes (Table 2). THC has been reported to inhibit the activity of other CYPs in human liver microsomes and recombinant systems, with K_i values ranging from 1.3 μM (CYP2C9) to 29 μM (CYP2A6) (Tables 2, 3). THC also has shown time-dependent inhibition of CYP1A1 and CYP2A6 activity in recombinant systems with similar efficiency (k_{inact}/K_I, ~0.02 $min^{-1}·μM^{-1}$) (Table 4).

Like THC, CBD has been reported to inhibit the activity of many CYPs, showing the highest potency toward 7-ethoxyresofurin O-deethylation by both human liver microsomes (Table 2) and recombinant CYP1A1 (Table 3). CBD also showed time-dependent inhibition of 7-ethoxyresorufin O-deethylation by recombinant CYP1 enzymes, with highest efficiency toward CYP1A2 (k_{inact}/K_I, 0.18 versus ≤ 0.05 $min^{-1}·μM^{-1}$, respectively) (Table 4). CBN was the most efficient time-dependent inhibitor of 7-ethoxyresorufin O-deethylation by recombinant CYP1A1 (k_{inact}/K_I, 0.21 $min^{-1}·μM^{-1}$) (Table 4). The resorcinol moiety of 7-ethoxyresorufin has been implicated in the generation of a reactive intermediate (Yamaori, Okushima, Yamamoto, & Watanabe, 2014). Pre-incubation of human liver microsomes with CBD (64 μM) decreased formation of CYP3A-mediated THC and cyclosporine metabolites, but not CYP2C9-mediated THC metabolites (Jaeger, Benet, & Bornheim, 1996). Additional studies are needed to assess the time-dependent inhibition kinetics of these cannabinoids toward CYP3A and other CYPs.

In vitro assays used to date to characterize the inhibition kinetics of THC, CBD, and CBN carry a major limitation. Based on the absence of data on non-specific binding of the cannabinoids, many published investigations of CYP-mediated cannabinoid-drug interactions did not account for experimental factors such as poor aqueous solubility of cannabinoids and extensive non-specific binding of cannabinoids to assay materials (e.g., microsomal proteins, glassware, and plasticware). Thus, reported K_i or IC_{50} values may be overestimated, leading to underestimation of the true interaction potential. These inaccuracies were addressed via in vitro-to-in vivo extrapolation using the predicted concentrations of THC and CBD in the intestine, as well as unbound plasma concentrations in the portal venous and systemic circulation, after administration of representative medical doses by various routes (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Lile, Kelly, Charnigo, Stinchcomb, & Hays, 2013) (Tables 5, 6). Unbound plasma concentrations were estimated using a conservative unbound fraction ($f_{u,p}$) of 0.03, based on plasma protein binding of THC (Garrett & Hunt, 1974; Klausner et al., 1975; Widman, Agurell, Ehrnebo, & Jones, 1974). Because values for non-specific binding of cannabinoids to assay materials were not available, $f_{u,p}$ was used as a surrogate to correct the reported K_i or IC_{50} values.

These predictions generally indicated a high potential for first-pass marijuana-drug interactions precipitated by THC and CBD after oral administration due to inhibition of CYPs expressed in the intestine and liver. CBD showed a higher potential than THC to precipitate systemic drug interactions after oral administration or inhalation. In summary, orally administered THC (40 mg) was predicted to inhibit intestinal

Table 2
Inhibition of cytochrome P450 activities in human liver microsomes by cannabinoids.

Enzyme(s)	Substrate	Reaction	Cannabinoid (μM)						Reference
			THC		CBD		CBN		
			K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	
CYP1A/1B1	7-Ethoxyresorufin	O-deethylation	4.7	–	1.8	–	0.081	–	(Yamaori, Kushihara et al., 2010)
CYP2D6	Dextromethorphan	O-demethylation	–	23	2.4	–	–	25	(Yamaori, Okamoto et al., 2011)
CYP2C9	(S)-Warfarin	7-hydroxylation	1.5	–	5.6	–	0.9	–	(Yamaori, Koeda et al., 2012)
CYP2C9	Diclofenac	4′-hydroxylation	1.3	–	9.9	–	1.3	–	
CYP3A4/5	Diltiazem	N-demethylation	–	–	6.1	–	–	–	(Yamaori, Ebisawa et al., 2011)

Dashes indicate data were not available.

CYP3A4 and CYP3A5, as well as hepatic CYP1B1, CYP2B6, CYP2C9, and CYP2C19, during first passage through the intestine and liver; systemic interactions also were predicted for these four hepatic CYPs (Table 5). Orally administered CBD (1500 mg) was predicted to inhibit all of the evaluated CYPs during first pass and to inhibit all but CYP1B1 and CYP2A6 systemically (Table 6). Inhaled THC (34 mg) was predicted to precipitate systemic interactions by inhibiting all evaluated CYPs except CYP3A4 and CYP3A5, whereas inhaled CBD (20 mg) was predicted to precipitate systemic interactions by inhibiting all evaluated CYPs except CYP2A6. Well-designed clinical studies are needed to test the accuracy of these predictions.

6.1.2. Interactions with UDP-glucuronosyltransferases (UGTs)

CBD was reported to inhibit ethanol glucuronidation, catalyzed largely by UGT1A9 and UGT2B7, in human liver microsomes, with a K_i of 3.1 mg/L (67 μM) (Al Saabi et al., 2013). In contrast, CBN at 5, 10, and 15 mg/mL (16, 32, and 48 μM) increased ethanol glucuronidation in a concentration-dependent manner, by approximately 2.5- to 6-fold relative to control. CBD and CBN (15 mg/mL) were further reported to inhibit ethanol glucuronidation by recombinant UGT1A9, by ~35–50% relative to control (Al Saabi et al., 2013). CBD also inhibited ethanol glucuronidation by recombinant UGT2B7, by 70%, whereas CBN increased activity by 4.2-fold. All of these effects required supraphysiological concentrations of CBD and CBN, suggesting UGT-mediated cannabinoid-ethanol interactions are unlikely to occur in vivo. However, the effects of cannabinoids on other UGT substrates, e.g., some opioids and benzodiazepines, remain to be determined, both in vitro and in vivo.

6.1.3. Interactions with transporters

Cannabinoids are both substrates and inhibitors of drug transporters (Table 7). Studies in mice showed THC to be a substrate for P-gp (Abcb1) in the gut and for both P-gp and Bcrp (Abcg2) at the blood-brain barrier. Abcb1a/b and Abcg2 knockout mice showed up to a 4.2- and 6.1-fold increase in the brain/blood THC ratio, respectively, compared to wild-type mice. Similarly, P-gp deficient CF1 mice demonstrated a 2.2-fold higher systemic AUC of THC compared to wild-type mice (Bonhomme-Faivre et al., 2008). Unlike THC, CBD was shown not to be a substrate for P-gp and Bcrp, as evidenced by lack of differences in the brain/blood CBD ratios between Abcb1a/b and Abcg2 knockout mice and wild-type mice (Brzozowska et al., 2016).

THC, CBD, and CBN (10 μM) had no inhibitory effects on P-gp activity (rhodamine 123 accumulation) relative to vehicle in the human T lymphoblastoid leukemia cell line CEM/VLB$_{100}$ after a 1-h exposure (Holland et al., 2006) (Table 7). A subsequent study by the same investigators showed that, relative to vehicle-treated cells, a 4-h (but not an 8- or 48-h) exposure to THC or CBD (10 μM) led to an increase in MDR1 (ABCB1) mRNA expression by 2–2.5 fold and a decrease in rhodamine 123 accumulation (Arnold, Hone, Holland, & Allen, 2012). However, a 72-h exposure to either cannabinoid decreased P-gp expression by up to 50% in a dose-dependent manner; the decrease in protein expression was accompanied by an increase in rhodamine 123 accumulation. Mice treated with THC (1 mg/kg) daily for 14 days showed an increase in P-gp localization in brain microvessels compared to control mice, which led to a 25–50% decrease in brain accumulation of the P-gp substrate risperidone (Brzozowska et al., 2017). These in vitro-in vivo incongruities with THC may be due to species differences in P-gp regulation and/or differences in transport properties between substrates.

THC, CBD, and CBN increased intracellular accumulation of the BCRP/Bcrp probe substrate mitoxantrone in the mouse MEF3.8/Bcrp1 cell line and inhibited basal and substrate (sulfasalazine)-stimulated ATPase activity in human BCRP-containing membranes (Holland, Lau, Allen, & Arnold, 2007) (Table 7), indicating inhibition of BCRP/Bcrp activity by these cannabinoids. Likewise, compared to vehicle, CBD (15 μM) increased the fetal-to-maternal ratio of the BCRP substrate glyburide by

Table 3
Inhibition of cytochrome P450 activities in recombinant enzymes or transfected cell systems by cannabinoids.

Enzyme	Substrate	Reaction	Cannabinoid (μM)						Reference
			THC		CBD		CBN		
			K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	
CYP1A1	7-Ethoxyresorufin	O-deethylation	4.8	–	0.16	–	0.54	–	(Yamaori, Kushihara et al., 2010)
CYP1A2			7.5	–	2.7	–	0.08	–	
CYP1B1			2.5	–	3.6	–	0.15	–	
CYP2A6	Coumarin	7-hydroxylation	29	–	55	–	40	–	(Yamaori, Ebisawa et al., 2011; Yamaori, Maeda et al., 2011)
CYP2B6	7-Benzoxyresorufin	O-debenzylation	2.8	–	0.69	–	2.6	–	
CYP2D6	Dextromethorphan	O-demethylation	–	17	2.7	–	–	12	(Yamaori, Ebisawa et al., 2011; Yamaori, Maeda et al., 2011)
CYP2D6	AMMC	O-demethylation	–	21	1.2	–	–	24	
CYP2C9	(S)-Warfarin	7-hydroxylation	1.4	–	1.0	–	0.9	–	(Yamaori, Koeda et al., 2012)
	Diclofenac	4′-hydroxylation	1.4		2.3		1.3		
CYP2C19	(S)-Mephenytoin	4′-hydroxylation	1.93	–	0.79	–	–	–	(Jiang, Yamaori, Okamoto, Yamamoto, & Watanabe, 2013)
CYP3A4	Diltiazem	N-demethylation	–	>50	1.0	–	–	>50	(Yamaori, Ebisawa et al., 2011)
CYP3A5			–	36	0.2	–	–	>50	
CYP3A7			–	30	12	–	–	24	

Table adapted from (Stout & Cimino, 2014; Zendulka et al., 2016). Dashes indicate data were not available. AMMC, 3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin iodide.

Table 4
Time-dependent inhibition of recombinant cytochrome P450 activity by cannabinoids.

Enzyme	Substrate	Reaction	THC			CBD[a]			CBN			Reference
			K_I (μM)	k_{inact} (min^{-1})	k_{inact}/K_I (min^{-1} μM^{-1})	K_I (μM)	k_{inact} (min^{-1})	k_{inact}/K_I (min^{-1} μM^{-1})	K_I (μM)	k_{inact} (min^{-1})	k_{inact}/K_I (min^{-1} μM^{-1})	
CYP1A1	7-Ethoxyresorufin	*O*-deethylation	1.2	0.023	0.019	5.9	0.316	0.054	0.09	0.019	0.21	(Yamaori, Kushihara et al., 2010)
CYP1A2			–	–	–	0.59	0.109	0.19	–	–	–	
CYP1B1			–	–	–	3.1	0.027	0.0087	–	–	–	
CYP2A6	Coumarin	7-hydroxylation	0.86	0.017	0.020	–	–	–	1.01	0.0091	0.0090	(Yamaori, Ebisawa et al., 2011; Yamaori, Maeda et al., 2011)

[a] Also showed time-dependent inhibition of 7-ethoxyresorufin *O*-deethylation in human liver microsomes (k_{inact}, 0.152 min^{-1}; K_I, 2.1 μM). Dashes indicate data were not available.

1.4-fold in a perfused human placenta model, indicating increased placental transport of glyburide via BCRP inhibition (Feinshtein et al., 2013). The same study showed, compared to vehicle-treated cells, CBD to inhibit mitoxantrone uptake in the human placenta cell line BeWo, with IC_{50} values ranging from 20 to 40 μM. Further studies in BeWo cells following a 72-h exposure to CBD (15 μM) demonstrated an increase in BCRP expression by 2-fold and a decrease in P-gp expression by >50% (Feinshtein, Erez, Ben-Zvi, Eshkoli, et al., 2013). Lastly, THC, CBD, and CBN increased the intracellular accumulation of the MRP1 substrates Fluo3 and vincristine in human 2008/MRP1/ABCC ovarian carcinoma cells, with IC_{50}s ranging from 30 to 110 μM (Holland, Allen, & Arnold, 2008).

The above observations suggest that cannabinoids can inhibit BCRP and MRP1 activity, decrease protein expression of P-gp, and increase protein expression of BCRP. However, the concentrations used in these experiments greatly exceeded systemic concentrations likely to be observed in humans, suggesting systemic transporter-mediated drug interactions with cannabinoids are unlikely. However, transporter-mediated interactions may be possible during first-pass through the intestine and/or liver upon oral administration. The effects of cannabinoids on other efflux transporters, as well as uptake transporters, have not been reported.

6.2. Human clinical drug interactions

Despite the widespread use and availability of marijuana products, substantive deficiencies remain regarding the potential risks for marijuana or cannabinoids to precipitate interactions with conventional drugs. Well-designed clinical studies are particularly sparse, and the few published studies to date involved CYPs as potential targets. For example, oral administration of CBD (Epidiolex®) (5–25 mg/kg/day) to patients with refractory epilepsy (aged 4–19 years) receiving the anti-seizure drug, clobazam, led to a profound increase (500 ± 300%) in mean (± SD) plasma concentrations of the active metabolite *N*-desmethylclobazam compared to baseline (absence of CBD) (Geffrey, Pollack, Bruno, & Thiele, 2015). After dosage adjustment of clobazam, due to reports of sedation, *N*-desmethylclobazam concentrations remained higher (by two- to sixfold) at eight weeks compared to baseline. This pharmacokinetic interaction was attributed to CBD-mediated inhibition of CYP2C19, which catalyzes the metabolism of *N*-desmethylclobazam (Gaston & Szaflarski, 2018; Geffrey et al., 2015).

Older studies substantiate the likelihood of pharmacokinetic interactions between cannabinoids and CYP substrates. A study published in 1978 showed the mean clearance of theophylline, a CYP1A2 substrate, to be approximately 40% higher in both habitual smokers of marijuana

Table 5
Predicted cytochrome P450-mediated clinical drug interaction potential of THC administered orally or by inhalation.a, b

Enzyme	IC_{50} or K_i corrected for binding (μM)[b]	Oral Dose (40 mg)			Inhaled Dose (34 mg)	Reference
		AUCR$_{gut}$	AUCR$_{hep}$	AUCR$_{sys}$	AUCR$_{sys}$	
CYP1A1	0.14	N/A	1.15	1.01	1.11	(Yamaori et al., 2010)
CYP1A2[a]	0.23	N/A	1.10	1.01	1.07	(Yamaori et al., 2010)
CYP1B1	0.074	N/A	1.30	1.03	1.21	(Yamaori et al., 2010)
CYP2A6	0.87	N/A	1.03	1.00	1.02	(Yamaori et al., 2011)
CYP2B6	0.084	N/A	1.26	1.02	1.18	(Yamaori et al., 2011)
CYP2D6	0.51	N/A	1.04	1.00	1.03	(Yamaori et al., 2011)
CYP2C9[a]	0.041	N/A	1.53	1.05	1.37	(Yamaori et al., 2012)
CYP2C19[a]	0.057	N/A	1.38	1.03	1.27	(Jiang et al., 2013)
CYP3A4	>1.5	>340	1.01	1.00	1.00-1.01	(Yamaori et al., 2011)
CYP3A5	1.1	480	1.02	1.00	1.01	(Yamaori et al., 2011)

Predicted potential for drug interactions mediated by inhibition of cytochromes P450 by THC consumed orally or inhaled. Predicted AUC ratio (AUCR) for intestine (AUCR$_{gut}$) ≥ 11, liver (AUCR$_{hep}$) ≥ 1.25, and systemic circulation (AUCR$_{sys}$) ≥ 1.02 indicate strong presystemic intestinal, presystemic hepatic, or systemic drug interaction potential, respectively. Values in shaded cells exceed the cut-off values recommended by the FDA (FDA, 2017).

● AUCR$_{gut}$ = 1 + (I$_g$/binding corrected K$_i$ or IC$_{50}$), where intestinal luminal concentration (I$_g$) was calculated as dose/250 mL (507,200 nM).

● AUCR$_{hep}$ = 1 + (I$_{hep,u}$/K$_i$ or IC$_{50}$), where I$_{hep,u}$ was calculated as 22 nM [$f_{u,p}$ × (C$_{max}$ + $\frac{F_a \times k_a \times Dose}{Q_{hep}/R_B}$)], where C$_{max}$ = 64 nM (Lile et al., 2013); F$_a$ = 1 (estimated based on FDA guidance), k$_a$ = 0.02 min^{-1} (estimated using Phoenix WinNonlin and confirmed by (Heuberger et al., 2015)), Q$_{hep}$ (liver blood flow) = 1500 mL/min (assumption), R$_B$ (blood:plasma ratio) = 0.4 (Schwilke et al., 2009).

● AUCR$_{sys}$ = 1 + (I$_{sys}$/K$_i$ or IC$_{50}$), where I$_{sys}$ = C$_{max,u}$ = 1.91 nM (orally) (Lile et al., 2013) or 15.5 nM (inhalation) (Huestis, Henningfield, & Cone, 1992).

a. Clinical studies suggest the potential for marijuana-drug interactions.

b. Published K$_i$ or IC$_{50}$ values (Table 3) corrected for non-specific binding to assay materials using f$_{u,p}$ = .03 (based on plasma protein binding of THC) as a surrogate (Garrett & Hunt, 1974; Klausner et al., 1975; Widman et al., 1974; Yamaori, Maeda et al., 2011).

Table 6
Predicted cytochrome P450-mediated clinical drug interaction potential of CBD administered orally or by inhalation.a, b

Enzyme	IC$_{50}$ or K$_i$ corrected for binding (μM)^b	Oral Dose (1500 mg)			Inhaled Dose (20 mg)	Reference
		AUCR$_{gut}$	AUCR$_{hep}$	AUCR$_{sys}$	AUCR$_{sys}$	
CYP1A1	0.0047	N/A	176	1.35	3.21	(Yamaori et al., 2010)
CYP1A2^a	0.081	N/A	11	1.02	1.13	(Yamaori et al., 2010)
CYP1B1	0.11	N/A	8.5	1.01	1.09	(Yamaori et al., 2010)
CYP2A6	1.65	N/A	1.5	1.00	1.01	(Yamaori et al., 2011)
CYP2B6	0.021	N/A	40	1.08	1.49	(Yamaori et al., 2011)
CYP2D6	0.081	N/A	11	1.02	1.13	(Yamaori et al., 2011)
CYP2C9^a	0.069	N/A	13	1.02	1.15	(Yamaori et al., 2012)
CYP2C19^a	0.024	N/A	35	1.07	1.43	(Jiang et al., 2013)
CYP3A4	0.030	6.3 x 10^5	28	1.05	1.34	(Yamaori et al., 2011)
CYP3A5	0.0059	3.2 x 10^6	140	1.28	2.76	(Yamaori et al., 2011)

Predicted potential for drug interactions mediated by inhibition of cytochromes P450 by CBD consumed orally or inhaled. Predicted AUC ratio (AUCR) for the intestine (AUCR$_{gut}$) ≥ 11, liver (AUCR$_{hep}$) ≥ 1.25, and systemic circulation (AUCR$_{sys}$) ≥ 1.02 indicate strong presystemic intestinal, presystemic hepatic, or systemic dug interaction potential, respectively. Values in shaded cells exceed the cutoff values recommended by the FDA (FDA, 2017).

I_g (intestinal luminal concentrations) = Dose/250 mL (1.90 × 10^7 nM), $I_{hep,u}$ = 815 nM, and $I_{sys,u}$ = 1.62 nM (oral) or 10.3 nM (inhalation).

● AUCR$_{gut}$ = 1 + (I_g/binding corrected K_i or IC$_{50}$).

● AUCR$_{hep}$ = 1 + ($I_{hep,u}/K_i$ or IC$_{50}$), where $I_{hep,u} = f_{u,p} \times (C_{max} + \frac{F_a \times k_a \times Dose}{Q_{hep}} / R_B)$, where C$_{max}$ = 54 nM (Bergamaschi et al., 2011); F$_a$ = 1 (estimated based on FDA guidance), k$_a$ = 0.02 min^{-1}

(estimated using Phoenix WinNonlin and confirmed by (Heuberger et al., 2015)), Q$_{hep}$ (liver blood flow) = 1500 mL/min (assumption), R$_B$ (blood:plasma ratio) = 0.4 (Heuberger et al., 2015; Schwilke et al., 2009).

● AUCR$_{sys}$ = 1 + (I_{sys}/K_i or IC$_{50}$), where I_{sys} = C$_{max,u}$ = 1.62 nM (THC, oral) (Fusar-Poli et al., 2009) and 10.3 nM (THC, inhalation) (Ohlsson et al., 1986).

a. Clinical studies suggest the potential for marijuana-drug interactions.

b. Published K$_i$ or IC$_{50}$ values (Table 3) corrected for non-specific binding to assay materials using f$_{u,p}$ = .03 (based on plasma protein binding of THC) as a surrogate (Garrett & Hunt, 1974; Klausner et al., 1975; Widman et al., 1974; Yamaori, Maeda et al., 2011).

cigarettes and of tobacco cigarettes compared to non-smoking control subjects (~73 versus 52 mL/kg/h) (Jusko, Schentag, Clark, Gardner, & Yurchak, 1978). These observations suggested that marijuana smoking may induce CYP1A2, similar to tobacco smoking. A study published in 1980 involving healthy male marijuana users administered oral CBD (600 mg/day for 5–12 days) with a single oral dose of hexobarbital (500 mg) exhibited a 36% reduction in apparent oral clearance and a 51% increase in the AUC of hexobarbital (Benowitz, Nguyen, Jones, Herning, & Bachman, 1980), a substrate for CYP2C19 (Knodell, Dubey, Wilkinson, & Guengerich, 1988). These data suggested inhibition of CYP2C19 by CBD, consistent with the more recent observations with N-desmethylclobazam (Geffrey et al., 2015).

Other clinical studies failed to show an effect of oral THC on the pharmacokinetics of drugs administered intravenously, specifically cyclophosphamide (CYP2B6/CYP2C9/CYP3A substrate), docetaxel (CYP1B1/CYP2B6/CYP3A substrate), doxorubicin (carbonyl reductase 1/P-gp substrate), and irinotecan (CYP3A/UGT1A1 substrate) (Bertholee, Maring, & van Kuilenburg, 2016; Ekhart et al., 2008; Kosel et al., 2002; Lal, Mahajan, Chen, & Chowbay, 2010; Riggs Jr. et al., 1981; Roy, Yu, Crespi, & Waxman, 1999; Solas et al., 2007). Consumption of 200 ml of marijuana tea containing 18% THC and 0.8% CBD (amount of each cannabinoid not specified) for 15 days also showed no effect on the pharmacokinetics of intravenous irinotecan and docetaxel (Engels et al., 2007). Likewise, THC-containing cigarettes and oral THC (as dronabinol) had no effect on the pharmacokinetics of oral indinavir (CYP3A/P-gp substrate) and nelfinavir (CYP2C19/CYP3A/P-gp substrate). As nelfinavir is a substrate for CYP2C19, the lack of an interaction contrasts with the aforementioned studies involving N-desmethylclobazam and hexobarbital; however, the contribution of CYP2C19 to nelfinavir clearance is inconclusive (Damle et al., 2009; Hirt et al., 2008; Kattel et al., 2015).

One case report described a probable interaction between smoked marijuana and warfarin (Yamreudeewong, Wong, Brausch, & Pulley, 2009). In brief, a 56-year-old white man who had been taking warfarin

for 11 years since undergoing surgery for mechanical heart valve replacement was admitted to the hospital due to upper gastrointestinal bleeding. Upon admission, his International Normalized Ratio (INR) was supratherapeutic (10.4). He was administered oral vitamin K, and his INR decreased to 1.8 the next day. He was discharged seven days after admission. Fifteen days later, he was readmitted due to a constant nosebleed and increased bruising, with an INR of 11.6. After treatment, he was discharged with an INR of 1.14. The patient mentioned smoking marijuana more frequently throughout these two hospitalizations due to depression. After counseling by the pharmacist about a potential marijuana-warfarin interaction, he stopped smoking marijuana. During the nine months when he did not smoke marijuana, his INR ranged from 1.08 to 4.4, with no major bleeding complications. Potential mechanisms of this probable interaction, which was based on the Horn Drug Interaction Probability Scale, included inhibition of CYP2C9-mediated warfarin metabolism and, to a lesser extent, displacement of warfarin from plasma protein binding sites by marijuana constituents.

Epidiolex® was recently approved by the United States Food and Drug Administration for treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients aged two years and older (Greenwich Biosciences, Inc., 2018). The labeling states a risk of drug interactions with substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 (Greenwich Biosciences, Inc., 2018). With the exception of CYP2C19 and possibly CYP2C9, these potential risks are based on in vitro predictions. Accordingly, opportunities exist to confirm or refute these predictions via controlled clinical studies.

7. Conclusions

The risk of marijuana-drug interactions precipitated by cannabinoids remains challenging to study due to the Schedule I classification of marijuana and marijuana products, the diversity of marijuana strains and derivative products on the commercial market, and the variety of

Table 7
Cannabinoid interactions with drug transporters.

Cannabinoids as substrates for efflux transporters

Transporter	Cannabinoid	Dose or Concentration	Experimental system(s)	Key observations	Reference
P-gp	THC	25 mg/kg (oral)	Mice	2× higher AUC in CF1 (P-gp-deficient) mice compared to wild type mice	(Bonhomme-Faivre et al., 2008)
	THC	3 mg/kg (ip)	Mice	1.5–4.2× higher brain/blood THC ratio in $Abcb1a/b^{(-/-)(-/-)}$ mice compared to wild type mice	(Spiro et al., 2012)
	CBD	10 mg/kg (sc)	Mice	Brain/blood CBD ratio in $Abcb1a/b^{(-/-)}$ mice was not different from that in wild type mice	(Brzozowska et al., 2016)
	CBN	1–100 µM	Human P-gp membranes	P-gp ATPase activity was stimulated, with $Cl_{int} = 0.7$ $min^{-1} \times 10^{-3}$	(Zhu et al., 2006)
Bcrp	THC	3 mg/kg (ip)	Mice	1.9–6.1× higher brain/blood THC ratio in $Abcg2^{(-/-)}$ mice compared to wild type mice	(Spiro et al., 2012)
	CBD	10 mg/kg (sc)		Brain/blood CBD ratio was similar between $Abcg2^{(-/-)}$ and wild type mice	(Brzozowska et al., 2016)

Cannabinoids as inhibitors of efflux transporters

Transporter	Cannabinoid	Probe Substrate	Experimental system(s)	Key observations	Reference
P-gp	THC, CBD, CBN	Rhodamine 123	Human CEM/VLB$_{100}$ cells	No increase in rhodamine 123 accumulation in the presence of cannabinoid (10 µM) after a 1-h exposure	(Holland et al., 2006)
	CBD	Verapamil, Rhodamine 123	Human P-gp membranes; LLC-PK1/MDRI cells	$IC_{50} = 39.6$ µM for verapamil-stimulated P-gp ATPase activity in human P-gp membranes. $IC_{50} = 8.44 \pm 0.58$ µM for rhodamine 123 accumulation in LLC-PK1/MDRI cells	(Zhu et al., 2006)
	THC, CBN	Verapamil	Human P-gp membranes	No inhibition of P-gp ATPase activity	(Zhu et al., 2006)
	THC	Risperidone, Clozapine	Mice	Decreased brain accumulation of risperidone (~25–50%) and 9-OH-risperidone (~33–63%) in mice treated with 1 mg/kg THC ip for 14 days followed by a 14-day wash-out. Repeated THC exposure did not impact clozapine (a non P-gp substrate) neurobehavioral effects.	(Brzozowska et al., 2017)
BCRP/Bcrp	THC, CBD, CBN	Sulfasalazine, Mitoxantrone	Human BCRP membranes; Murine MEF3.8/Bcrp1 cells	IC_{50} values for sulfasalazine-stimulated ATPase activity ranged from 4.4–7.3 µM. Mitoxantrone toxicity (IC_{50}) in MEF3.8/Bcrp1 cells was significantly reduced to 2 µM (THC) and 5 µM (CBD and CBN).	(Holland et al., 2007)
	CBD	Mitoxantrone, Glyburide	Human CEM/VLB$_{100}$ cells, BeWo cells, Jar cells; Human perfused placenta	Significant increase in mitoxantrone accumulation following exposure to 10 µM CBD in BeWo, Jar, and MCF7/P-gp cell lines. CBD (15 µM) increased glyburide fetal-to-maternal ratio 1.4-fold in human perfused placenta.	(Feinshtein, Erez, Ben-Zvi, Erez, et al., 2013)
MRP1	CBD, CBN, THC	Fluo3, Vincristine	2008/MRP1 cells	IC_{50} for Fluo3 accumulation: CBD = 128 µM, CBN = 145 µM, THC = 161 µM. IC_{50} for vincristine accumulation: CBD = 38 µM, CBN = 30.9 µM, THC = 107 µM	(Holland et al., 2008)

Effects of cannabinoids on efflux transporter expression

Transporter	Cannabinoid	Dose or concentration	Experimental system(s)	Key observations	Reference
P-gp	CBD, THC	0.1, 1, 10 µM	Human CEM/VLB$_{100}$ cells	P-gp expression increased by 50% after a 72-h exposure.	(Holland et al., 2006)
	CBD, THC	10 µM	Human CEM/VLB$_{100}$ cells	*MDR1* mRNA expression increased by 2 and 2.5 fold, respectively, at a 4-h, but not 8- or 48-h, incubation.	(Arnold et al., 2012)
	CBD	15 µM	BeWo cells, Jar cells, MCF7/P-gp cells	A 72-h exposure resulted in ~60% decrease in P-gp expression in BeWo and Jar cell lines but a ~2.5 fold increase in P-gp expression in MCF7/P-gp cell line.	(Feinshtein, Erez, Ben-Zvi, Erez, et al., 2013)
	THC	1 mg/kg THC ip for 14 days followed by 14 day wash-out	Mice	Increased expression of P-gp in the ventrolateral septum, nucleus accumbens core, and the paraventricular nucleus of the thalamus	(Brzozowska et al., 2017)
BCRP	THC, CBD, CBN	0.4, 4, 5 µM	WiDr human colon cells, MEF3.8/BCRP cells	No change in ABCG2 (BCRP) expression	(Holland et al., 2007)
	CBD	15 uM	BeWo cells, Jar cells	A 72-h exposure resulted in ~2 fold increase of BCRP expression in BeWo and Jar cell lines.	(Feinshtein, Erez, Ben-Zvi, Erez, et al., 2013)

routes of administration. However, the sheer magnitude of forensic and academic literature on marijuana, its constituents, and its drug interaction potential collectively presents a useful primer for designing and executing future studies on this critical, understudied public health issue.

Results from the few available clinical studies indicate a risk for marijuana-drug interaction mediated via inhibition of hepatic CYP2C19 by THC and CBD. Additionally, one case report suggested a risk for an interaction mediated via inhibition of hepatic CYP2C9 by marijuana constituents. Finally, in vitro-in vivo extrapolation suggested a risk for interactions mediated via inhibition of intestinal CYP3A and

hepatic CYP1B1, CYP2B6, CYP2C9, and CYP2C19 by THC and CBD and of hepatic CYP1A1, CYP1A2, CYP2A6, CYP2D6, and CYP3A by CBD (Tables 5, 6). To date, in vitro and clinical studies evaluating marijuana-drug interactions have focused predominately on the CYPs as interaction targets. Effects of marijuana and its constituents on other drug metabolizing enzymes (e.g., the UGTs) remain less characterized. Regarding drug transporters, in vitro and animal studies have thus far focused exclusively on efflux transporters, specifically P-gp, BCRP, and MRP1. The effects of cannabinoids on other efflux, as well as uptake, transporters remain a critical knowledge gap, particularly as

the lipophilic cannabinoids tend to accumulate in tissues upon chronic marijuana use.

Another understudied problem is that of potential marijuana-drug interactions precipitated in lung tissue via inhalation of marijuana. For example, THC and other constituents in marijuana smoke, such as polycyclic aromatic hydrocarbons, which activate the aryl hydrocarbon receptor, may induce lung CYP1A1 (Roth et al., 2001). This potential interaction would be particularly critical for pregnant women, in whom placental CYP1A activity can be altered by tobacco smoke (Stejskalova & Pavek, 2011). Such alterations may have implications for fetal growth and development.

In addition to the many gaps in scientific knowledge regarding marijuana-drug interactions, researchers face multiple legal and regulatory hurdles that preclude clinical, even in vitro, evaluation in a timely manner. Although THC and CBD are available as prescription drugs, the doses used typically are much less than the THC and CBD content in commercial products consumed for medical and recreational purposes. The widespread availability of these products highlights the urgent need for well-designed in vitro and clinical studies to investigate potential marijuana-drug interactions. This public health need should prompt the development of policies regarding marijuana research, with the end goal of informing health care providers and consumers about the safety of consuming marijuana products concomitantly with conventional medications.

Conflict of interest statement

The authors declare no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pharmthera.2019.05.001.

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