Clin Pharmacokinet (2016) 55:1353–1368
DOI 10.1007/s40262-016-0400-9

REVIEW ARTICLE

Pharmacokinetic Drug Interactions with Tobacco, Cannabinoids and Smoking Cessation Products

Gail D. Anderson[1] · **Lingtak-Neander Chan**[1]

Published online: 22 April 2016

Abstract Tobacco smoke contains a large number of compounds in the form of metals, volatile gases and insoluble particles, as well as nicotine, a highly addictive alkaloid. Marijuana is the most widely used illicit drug of abuse in the world, with a significant increase in the USA due to the increasing number of states that allow medical and recreational use. Of the over 70 phytocannabinoids in marijuana, Δ^9-tetrahydrocannabinol (Δ^9THC), cannabidiol (CBD) and cannibinol are the three main constituents. Both marijuana and tobacco smoking induce cytochrome P450 (CYP) 1A2 through activation of the aromatic hydrocarbon receptor, and the induction effect between the two products is additive. Smoking cessation is associated with rapid downregulation of CYP1A enzymes. On the basis of the estimated half-life of CYP1A2, dose reduction of CYP1A drugs may be necessary as early as the first few days after smoking cessation to prevent toxicity, especially for drugs with a narrow therapeutic index. Nicotine is a substrate of CYP2A6, which is induced by oestrogen, resulting in lower concentrations of nicotine in females than in males, especially in females taking oral contraceptives. The significant effects of CYP3A4 inducers and inhibitors on the pharmacokinetics of Δ^9THC/CBD oromucosal spray suggest that CYP3A4 is the primary enzyme responsible for the metabolism of Δ^9THC and CBD. Limited data also suggest that CBD may significantly inhibit CYP2C19. With the increasing use of marijuana and cannabis products, clinical studies are needed in order to determine the effects of other drugs on pharmacokinetics and pharmacodynamics.

Key Points

Both marijuana and tobacco smoking induce cytochrome P450 (CYP) 1A2 through activation of the aromatic hydrocarbon receptor, and the induction effect between the two products is additive.

CYP3A4 inducers and inhibitors significantly alter the pharmacokinetics of Δ^9-tetrahydrocannabinol (Δ^9THC), 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and cannabidiol (CBD) when administered as a Δ^9THC/CBD oromucosal spray, suggesting a major role of CYP3A4 in the elimination of Δ^9THC and CBD.

There are only limited data on the effects of other drugs on the disposition of marijuana and other cannabis products, and additional clinical studies are needed.

1 Introduction

Data from the World Health Organization (WHO) have shown that 21 % of the global population aged 15 years and above smoke tobacco. The prevalence of tobacco smoking is higher in men than in women, regardless of age. The Western Pacific region and Europe have the highest prevalence of tobacco smoking among men and women, at 48.5 and 19.3 %, respectively [1]. In the USA, 17.8 % of all adults (42.1 million people) were current smokers, according to data from the Centers for Disease Control and

✉ Gail D. Anderson
gaila@washington.edu

[1] Department of Pharmacy, Box 357630, University of Washington, Seattle, WA 98195, USA

Prevention, in 2013 [2]. This reflected a net reduction of 3.1 % from 2005. The prevalence was highest among adults between 25 and 44 years of age (20.1 %) and lowest among older adults over 64 years (8.8 %). It is well known that smoking is a leading cause of many preventable diseases and death. In the USA, marijuana use has doubled in the past decade, increasing from 4.1 % in 2001–2002 to 9.5 % in 2012–2013, primarily because of the increasing number of states allowing medical and recreational use of marijuana [3]. Globally, marijuana is the most widely used illicit drug of abuse in the world, with an estimated 2.6–5.0 % of people reported as having used cannabis at least once in the previous year [4].

2 Tobacco

Tobacco is derived from the plant *Nicotiana*, grown for production of the tobacco leaf. In addition to nicotine, tobacco smoke contains over 7000 chemicals in the form of metals, volatile gases and insoluble particles. Some of the documented carcinogens include aromatic amine, arsenic, benzene, benzo[a]pyrene, beryllium, butadiene, cadmium, polonium[120], nicotine and nicotine-derived nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN), and a number of other polycyclic aromatic hydrocarbons (PAHs) [5–7]. The use of tobacco products may interact with the effects of other drugs. Although the mechanisms of interaction between tobacco products and drugs may include both pharmacodynamic and pharmacokinetic interactions, the knowledge is more extensive and the mechanism is more established for the pharmacokinetic interactions. Specifically, PAHs, which are products of incomplete combustion of organic matter through tobacco smoking, are well-known inducers of drug-metabolizing enzymes. Exposure to PAHs in humans results in marked induction of cytochrome P450 (CYP) 1A1 and 1A2 in the liver, small intestine and lung tissues [8–10]. In addition to the CYP1A family, there are limited data suggesting induction of CYP2E1 by tobacco smoking, although it is unclear whether the induction is caused by PAHs or other components in the tobacco smoke, such as toluene [11–13]. CYP2A6 activity is suppressed by tobacco smoking, but this is not caused by nicotine, as previously proposed [14, 15]. Although there are some published data suggesting that PAHs may alter the expression of phase II enzymes and some drug transporters—namely, multidrug resistance protein 1 (MDR1) and multi-resistant protein (MRP)—these results are inconsistent with substrate concentrations, which are likely clinically relevant on the basis of current knowledge [16].

2.1 Mechanism of CYP1A Induction by Polycyclic Aromatic Hydrocarbons

The human CYP1A enzymes function both as detoxifying enzymes for drugs (e.g. caffeine, theophylline, *R*-warfarin) and as metabolic activators for harmful xenobiotics, such as aromatic amines and heterocyclic aromatic amines that have carcinogenic potential. Of the two isoforms that are expressed in humans, CYP1A2 is preferentially expressed and accounts for about 15 % of total hepatic CYP content. A low level of CYP1A2 expression is also present in the oesophagus, stomach and colon, but not in the small intestine. On the other hand, CYP1A1 is considered an extrahepatic enzyme in humans, expressed at low levels in the lung, gastrointestinal tract, kidney and placenta, but practically undetectable in the liver [17]. Both enzymes are regulated by the aromatic hydrocarbon receptor (AhR) and are highly inducible at both messenger RNA (mRNA) and protein levels by a variety of chemicals. The mechanism of induction through AhR has been well characterized. In brief, AhR is a ligand-activated transcription factor and a basic helix–loop–helix protein, which is coupled with two heat-shock proteins (Hsp90), a co-chaperone prostaglandin E synthase 3 (p23) and an AhR-associated protein 9 (ARA9). The binding of PAH to AhR results in the release of Hsp90 and the translocation of the AhR–PAH complex into the nucleus with the help of Ah receptor nuclear translocator (Arnt). This heterodimer then interacts with the xenobiotic responsive element at the promotor region of the *CYP1A1* and *CYP1A2* genes, which leads to transcription activation of the genes and increased translation of the specific CYP enzymes [18, 19]. Since the mRNA of AhR is dominantly expressed in the placenta, lung, heart, pancreas and liver, induction of CYP1A enzymes can occur through different routes of PAH exposure, including smoking [20, 21]. In addition to PAHs, endogenous hormones also appear to modulate the expression of CYP1A enzymes both under normal physiology and in the presence of diseases [18].

2.2 Pharmacokinetics of Nicotine and Effects of Other Drugs on Nicotine Metabolism

Nicotine is the main ingredient in tobacco products that leads to addiction. Besides nicotine, other alkaloids that are present in abundance in tobacco products include nornicotine, anatabine and anabasine [22, 23]. The plasma concentrations of anatabine and anabasine can be used to confirm whether the nicotine exposure of an individual comes from tobacco products or from nicotine replacement therapy, such as nicotine gum or nicotine transdermal patches.

Nicotine can be absorbed from various routes of administration, which include inhalation, buccal absorption and transdermal absorption. Nicotine is a weak base, with an acid dissociation constant (pKa) of 8.0. The absorption kinetics of nicotine through smoking are a complex process, as nicotine is both distilled from burning tobacco and carried proximally by particulate matter into the lower respiratory tract. The pH of the particulate matter in some commercially available cigarette brands ranges from 6.0 to 7.8, although the majority of the cigarette brands available in the USA are on the lower end of the pH range. The high systemic bioavailability of nicotine via smoking is likely facilitated by the efficient transfer of nicotine from the particle to the vapour phase and/or impacting of particles in the airways, which are covered with bronchial fluid at a pH of 7.4 [24]. Published data suggest that the bioavailability of nicotine through cigarette smoking is 80–90 %, whereas the bioavailability rates are about 55 or 70 % with use of a nicotine inhaler or nasal spray, respectively [25]. Nicotine gum has bioavailability of 51–78 %, and nicotine transdermal patches have bioavailability of 68–100 % [25]. The maximal pharmacodynamic effect of nicotine is achieved quickly through smoking, as the maximum plasma concentration (C_{max}) is achieved within 5 min after a cigarette is smoked [25].

After systemic absorption, nicotine undergoes extensive hepatic metabolism, primarily by CYP2A6. CYP2B6 and 2E1 also play a minor role in the biotransformation of nicotine [25]. The primary metabolite of nicotine is cotinine, with small fractions of the compound being converted to nicotine-*N*-oxide, nornicotine and 4-(3-pyridyl)-4-hydroxybutanoic acid, or being conjugated to nicotine glucuronide [26]. The majority of the cotinine is either glucuronidated by uridine diphosphate (UDP) glucuronosyltransferase (UGT) UGT1A4 and 1A9, or further metabolized by CYP2A6 to 3′-hydroxycotinine (3HC) [27]. UGT2B10 and 2B17 are the two key hepatic enzymes involved in the glucuronidation of 3HC for the formation of the two inactive metabolites, 3HC-*N*-glucuronide and *O*-glucuronide, respectively. Cotinine, 3HC and a few other nicotine metabolites, as well as other tobacco-based alkaloids such as anabasine, are present in the urine in large quantities [28]. Their urinary concentration profiles can be used to assess a person's adherence to a smoking cessation intervention.

CYP2A6 is polymorphically expressed. Specific genotypes (e.g. *CYP2A6**9/*9) are associated with up to a 50 % reduction in the rate of formation of 3HC [26]. Additionally, both UGT2B10 and 2B17 are polymorphically expressed [27, 29]. The deletion frequencies for the *UGT2B17* gene are approximately 50, 45 and 95 % among Caucasians, African Americans and Asians, respectively [30]. However, the ratio of 3HC to cotinine, also known as the nicotine-to-metabolite ratio, does not appear to be altered by UGT2B17 deletion alone [31]. In addition to nicotine pharmacokinetics, genetic polymorphism of these enzymes can also alter the pharmacodynamics of nicotine and may influence the risk of smoking-related cancer and nicotine addiction. The current knowledge of CYP2A6 is more extensive than that of UGT2B10 and 2B17. CYP2A6 is involved in the metabolism of a relatively small group of drugs [32, 33]. Over 35 alleles of CYP2A6 have been described so far. Generally speaking, Caucasians and Latinos metabolize nicotine faster than Asians and African Americans. Women also metabolize nicotine faster than men. Although the cause of nicotine addiction is multifactorial, studies have shown that a higher nicotine metabolic rate may contribute to a higher level of nicotine dependency. Therefore, one of the theoretical treatment approaches towards smoking cessation is to alter the activity of CYP2A6. Selegiline is a mechanism-based inhibitor of CYP2A6, and its role as a smoking cessation treatment has been evaluated in a few clinical trials, with inconsistent results [34–36]. At this point, altering the pharmacokinetic of nicotine alone is not an effective approach for smoking cessation or tobacco addiction.

2.3 Effects of Tobacco on Other Drugs

Since tobacco smoking induces the expression of CYP1A1 and 1A2 enzymes, drugs that are primarily metabolized by these enzymes will have faster systemic clearance as a result of enzyme induction (Table 1). As reviewed by Zevin and Benowitz [37], the average clearance rates of caffeine, chlorpromazine, clozapine, oestradiol, flecainide, fluvoxamine, haloperidol, mexiletine, olanzapine, propranolol, tacrine and theophylline were increased by 30–100 % in smokers compared with non-smokers.

Melatonin is metabolized by CYP1A2, with minor metabolism by CYP2C9 and CYP2C19 [38]. In a study assessing the effects of caffeine on the pharmacokinetics of melatonin 6 mg, the baseline clearance and elimination half-life ($t_{½}$) values of melatonin were 245 and 143 % higher, respectively, in six healthy male smokers than in six non-smokers [39]. Smoking did not significantly alter endogenous melatonin concentrations. The area under the plasma concentration–time curve (AUC) from time zero to infinity (AUC_{∞}) of a single dose of melatonin 25 mg increased 2- to 10-fold when it was administered to seven female smokers and one male smoker before and after a 7-day smoking abstinence period [40]. Mirtazapine is metabolized by CYP1A2, CYP2D6 and CYP3A4 [41]. The steady-state concentrations of mirtazapine were, on average, 23, 34 and 41 % lower in patients who were smokers than in non-smokers [42–44]. The AUC_{∞} value of tizanidine was 33 % lower in 15 healthy male smokers than in 38

Table 1 Highlight of clinically significant cytochrome P450 (CYP)–mediated pharmacokinetic drug interactions with tobacco, marijuana and cannabinoids, where these products serve as the precipitant drugs

Compound	CYP involved	Mechanism	Object drugs and impact on plasma concentration	References
PAHs from cigarette smoking	CYP1A1, CYP1A2	Induction	↓ Caffeine ↓ Chlorpromazine ↓ Clozapine ↓ Oestradiol ↓ Flecainide ↓ Fluvoxamine ↓ Haloperidol ↓ Melatonin ↓ Mexiletine ↓ Mirtazapine ↓ Olanzapine ↓ Propranolol ↓ Ropinirole ↓ Tacrine ↓ Theophylline ↓ Tizanidine	[39–47, 60]
Marijuana inhalation	CYP1A1, CYP1A2	Induction	↓ Chlorpromazine ↓ Theophylline	[89–92]
CBD	CYP2C19	Inhibition	↑ Clobazam ↑ *N*-Desmethylclobazam	[101]

CBD cannabidiol, *PAHs* polycyclic aromatic hydrocarbons

non-smokers [45] after a 4 mg single dose of tizanidine, which is metabolized primarily by CYP1A2 [46]. Tobacco smoking should also increase the clearance of ramelteon [47] and rasagiline, as both are extensively metabolized by CYP1A2 [48].

Clopidogrel irreversibly binds to P2Y12 adenosine diphosphate receptors and inhibits platelet function. It is a prodrug, which is first converted to 2-oxo-clopidogrel by CYP1A2, 2B6 and 2C19, and is eventually converted to the active metabolite by CYP2B6, 2C9, 2C19 and 3A4. Therefore, CYP2C19 and 3A4 are considered the most important enzymes for the biotransformation of clopidogrel [49]. However, a so-called smoking paradox has been observed in a number of clinical trials, which showed improved clinical responsiveness and enhanced achievement of clinical endpoints with clopidogrel therapy in smokers [50]. Yousef et al. [51] compared the single-dose (75 mg) pharmacokinetics of clopidogrel carboxylic acid metabolite in 27 smokers and 48 non-smokers. In comparison with non-smokers, the AUC_{∞} and $t_{½}$ values of the clopidogrel metabolite were 30 and 35 % lower, respectively, in smokers. Conversely, Gurbel et al. [52] showed that the AUC value of the clopidogrel active metabolite was 18.4 % higher in 54 smokers than in 56 non-smokers in a controlled clinical trial. A significantly greater extent of platelet inhibition, as measured by calculated inhibition of platelet aggregation, was also observed in smokers. At this point, further investigations are needed to understand the mechanism of this observed interaction.

Current research suggests that nicotine as a compound appears to have limited drug interaction potential. Nicotine exposure, in the absence of smoke, does not affect the activity of CYP1A2 in humans [53]. However, in a study of eight healthy subjects, application of a 17.5 mg transdermal nicotine patch at 12 h prior to oral administration of levodopa resulted in a 24 % reduction in the levodopa C_{max} [54]. The change in the AUC from 0 to 4 h (AUC_4) after levodopa dosing was not significant. The study was repeated using a higher nicotine dose (a 35 mg transdermal patch) in six male subjects receiving enteral nutrition (the components of the enteral formula and the feeding regimen were not mentioned). Levodopa absorption was reduced by an average of 34 % in six of the eight subjects and by 60 % in four of those six subjects [54]. The exact mechanism of this possible drug interaction is unclear, and the clinical significance requires confirmation with further investigation. It is worth noting that the oral bioavailability of levodopa is impaired by food, which may explain the reduced bioavailability in the subjects receiving enteral nutrition.

What is equally important is to determine how smoking cessation alone may alter the pharmacokinetics of existing drug regimens in a previously smoking individual. In a study involving eight men and four women who were heavy smokers (defined as smoking at least 20 cigarettes daily), CYP1A2 activity, measured by caffeine clearance, was decreased by 12.3, 20.1, 25.0 and 28.2 % from baseline after abrupt cessation of smoking for 1, 2, 3 and 4 days, respectively [55]. At steady state, the overall mean reduction in CYP1A2 activity was 36.1 % (range 24.4–58.4 %). All study subjects experienced significantly reduced caffeine clearance by day 6 of smoking cessation. The estimated $t_{½}$ of the CYP1A2 enzyme was 38.6 h. These results suggest that dose reduction may be necessary as early as the first few days after smoking cessation to prevent toxicity, especially for drugs with a narrow therapeutic index.

This time course of CYP1A2 downregulation upon smoking cessation is consistent with the time course of adverse event occurrence as presented in a number of published case reports. Bondolfi et al. [56] reported a case of clozapine toxicity with a new onset of severe sedation and fatigue 2 weeks after abrupt cessation of smoking. The symptoms were accompanied by a threefold increase in clozapine and norclozapine plasma concentrations. Similarly, Zullino et al. [57] reported a case of olanzapine neurotoxicity, with akathisia and bradyphrenia, 4 days after a patient reduced daily cigarette use from 40 cigarettes to 10. The symptoms progressed to Parkinson's syndrome, with bradykinesia, stooped posture, small steps, hypomimia, cogwheel rigidity, seborrhoea and a positive naseopalpebral reflex. The symptoms improved after the daily olanzapine dose was decreased by 33 %. Although the cause of the Parkinsonian symptoms in this case was likely multifactorial and not limited to reduction of smoking alone, the time course was still consistent with the study results published by Faber and Fuhr [50], in that a stepwise daily dose reduction of approximately 10 % until the fourth day after smoking cessation is likely necessary, accompanied by therapeutic drug monitoring where appropriate. In a case report [58], a woman treated with ropinirole for restless leg syndrome developed significant adverse effects, including profuse sweating at night, 4 days after quitting smoking.

In summary, smoking cessation results in downregulation of the CYP1A2 enzyme. The extent of enzyme downregulation varies and depends on the magnitude of the change in cigarette smoking in comparison with baseline. However, since the turnover time of the CYP1A2 enzyme is just under 2 days, a clinically significant effect can be detected within a week of smoking cessation. Empirical dose reduction may be necessary within 2–3 days after smoking cessation. In patients taking drugs with narrow therapeutics indices, close monitoring of clinical symptoms for adverse events is necessary within the first week of smoking cessation. Therapeutic drug monitoring, if available and clinically feasible, should be performed.

2.4 Effects of Other Drugs on Nicotine Metabolism

The number of published drug interaction studies aimed at evaluating nicotine as the object drug is very limited (Table 2). As mentioned, selegiline is a CYP2A6 inhibitor, which decreases the rate of nicotine metabolism, although the clinical implication of CYP2A6 inhibition is unknown [34]. Other documented in vivo CYP2A6 inhibitors include methoxsalen and tranylcypromine [23]. Fortunately, none of these agents is commonly prescribed in clinical practice. Since smoking is common among individuals with history of opioid abuse who undergo methadone maintenance treatment, a double-blind, randomized, placebo-controlled clinical trial was conducted to evaluate the potential pharmacokinetic and pharmacodynamic interaction between nicotine and methadone in 40 active smokers, who had been receiving a stable methadone regimen for at least 2 weeks (mean dose 81.1 mg/day) [59]. The study subjects received nicotine via their regular brand of cigarette on study day 1. Then, on days 2 and 3, they were randomized to receive either 4 mg of nicotine gum or placebo. The pharmacokinetics of plasma methadone, nicotine, cotinine and hydroxycotinine were compared. The pharmacodynamic parameters were also assessed through responses to a battery of subjective assessment tools, which included vital signs, a visual analogue scale for smoking and craving for cigarettes, a questionnaire on smoking urges, the Minnesota Nicotine Withdrawal Scale, Addiction Research Center Inventory, Profile of Mood States, and Subjective Opioid Withdrawal Scale. Each of the tools was administered four times, before and after nicotine administration, and before and 3 h after oral methadone administration. Overall, trough plasma methadone concentrations were unaffected by the method of nicotine exposure, even though plasma nicotine concentrations were significantly higher on the days when nicotine exposure occurred through smoking. Cigarette smoking also appeared to decrease opioid withdrawal scores by enhancing the effect of methadone. In addition, methadone administration significantly decreased nicotine withdrawal scores. These findings suggest that a pharmacodynamic interaction between nicotine and methadone may exist, whereas a pharmacokinetic interaction seems unlikely [59]. In vitro and in vivo data have suggested that the CYP2A6 enzyme can be induced by artemisinin carbamazepine, dexamethasone, phenobarbital, phenytoin and rifampin; however, the clinical significance is unclear [25, 60]. Finally, oestrogen induces CYP2A6 expression [61]. The systemic

Table 2 Highlight of clinically significant cytochrome P450 (CYP)–mediated pharmacokinetic drug interactions with tobacco, marijuana and cannabinoids, where these products serve as the object drugs

Object drug	Substrate of	Documented precipitant drugs	References
Nicotine	CYP2A6	Inducer of nicotine metabolism:	[25, 60]
		Artemisinin	
		Carbamazepine	
		Dexamethasone	
		Oestrogen (including combined hormonal contraceptive agents)	
		Inhibitor of nicotine metabolism:	
		Methoxsalen	
		Selegiline	
		Tranylcypromine	
Δ^9THC/CBD oral mucosal spray	CYP3A4	Inducer of Δ^9THC/CBD metabolism:	[103]
		Rifampin	
		Inhibitor of Δ^9THC/CBD metabolism:	[103]
		Ketoconazole	

CBD cannabidiol, *Δ⁹THC* Δ^9-tetrahydrocannabinol

clearance of nicotine is faster in women than in men, especially among women who use combined hormonal contraceptive agents [62–64]

3 Cannabinoids

Marijuana is derived from the plant *Cannabis sativa* L. and consists of a variety of compounds, including over 400 natural compounds, with the phytocannabinoids being the most psychologically active [65]. At least 70 phytocannabinoids have been identified in marijuana [66]. Δ^9-Tetrahydrocannabinol (Δ^9THC), cannabidiol (CBD) and cannibinol are the three main constituents. Δ^9THC binds to CB1 and CB2 receptors and is primarily responsible for the psychotropic effects. There has been significantly increased interest regarding the potential pharmacological effects of CBD for use as an antiepileptic, anxiolytic, antiemetic and hypnotic without the psychotropic effects of Δ^9THC. Mechanistically, CBD is a non-competitive antagonist of CB1 receptors, inhibiting CB1 activity through negative allosteric modulation [67], and an inverse agonist of CB2 receptors [68, 69]. CBD has also demonstrated anti-inflammatory activity in several preclinical models [69], partially mediated by the adenosine A2A receptor [70]. Cannabinol (CBN) has minimal reported pharmacological effects [66].

3.1 Pharmacokinetics

The bioavailability of Δ^9THC after oral or smoking administration is highly variable [66]. After a cigarette containing 19 mg of Δ^9THC (an estimated smoked amount of 13 ± 1.2 mg) was smoked, peak concentrations occurred within 1–3 min, with 8–25 % bioavailability in comparison with an 5 mg intravenous infusion [71]. On oral dosing of a cookie containing 2 mg of Δ^9THC, the bioavailability was 4–12 % because of extensive first-pass metabolism, with a time to reach the C_{max} (t_{max}) of 1–2 h [71]. Δ^9THC is primarily metabolized by CYP2C9 to an active metabolite, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) [72, 73]. The psychoactive properties of 11-OH-THC are equivalent to those of Δ^9THC [74]. CYP2C9 also has a major role in the further oxidation of 11-OH-THC to an inactive metabolite, 22-nor-9-carboxy-Δ^9-tetrahydrocannabinol (COOH-THC). After a single 15 mg oral dose of Δ^9THC, *CYP2C9**3 subjects ($n = 4$) had a 3-fold higher median Δ^9THC AUC value than *CYP2C9**1/*1 subjects ($n = 10$), with a trend towards increased sedation in subjects carrying the 3/*3 alleles [75]. The $t_{½}$ of Δ^9THC was approximately 7 h in *CYP2C9**1/*1, *1/*2 and *2/*2 subjects and was increased to 15 and 22 h in *1/*3 and *3/*3 genotypes, respectively. There was no effect of CYP2C9 polymorphism on plasma concentrations of 11-OH-THC. Because of slow redistribution of Δ^9THC from adipose tissue and other tissues, the terminal $t_{½}$ ranges from 20 to 36 h, although in most studies, the concentrations have been followed for only up to 72 h and there was low assay sensitivity at low concentrations, limiting the reliability of the estimates [66].

Dronabinol (Marinol®; Solvay Pharmaceuticals, Inc., Marietta, GA, USA) is a synthetic Δ^9THC indicated for weight loss in patients with acquired immune deficiency syndrome (AIDS) or for nausea and vomiting associated

with cancer chemotherapy in patients who have failed conventional antiemetic treatments. Dronabinol is almost completely absorbed, with a t_{max} of 0.5–4 h, and undergoes extensive first-pass metabolism to the active metabolite, 11-OH-THC, with low bioavailability of 2–14 % [76]. The concentrations of the parent and active metabolite are approximately equal. The terminal $t_{½}$ is 25–36 h, with the majority of the dose eliminated by biliary excretion.

CBD is extensively metabolized by CYP2C19 and CYP3A4 to eight monohydroxylated metabolites [77]. The pharmacokinetics of deuterium-labelled CBD was determined in five chronic marijuana smokers receiving 20 mg CBD intravenously and 18.8–19.4 mg by smoking. On oral dosing, the absorption of CBD was low (~6 %) because of extensive first-pass metabolism [78], with an estimated $t_{½}$ of 68 h (range 41–113 h) [79]. After inhalation of CBD, the bioavailability was 11–45 % [80].

Sativex® oromucosal spray (GW Pharma LT) is a combination of Δ^9THC and CBD approved for treatment of spasticity due to multiple sclerosis. Each 100 μL spray contains 2.7 mg of Δ^9THC and 2.5 mg of CBD, delivered underneath the tongue or to the inside of the cheek. The single- and multiple-dose pharmacokinetics of Δ^9THC and CBD were determined in 24 healthy male subjects who received THC/CBD spray as either 2, 4 or 8 single-dose or multiple-dose sprays for nine consecutive days [81]. The mean t_{max} values of Δ^9THC and CBD were approximately 1 h for all single and multiple doses. The $t_{½}$ values were 2.0, 3.7 and 5.3 h for Δ^9THC; 6.5, 8.8 and 8.1 h for 11-OH-THC; and 5.3, 6.4 and 9.4 h for CBD after administration of 2, 4 and 8 single-dose sprays, respectively.

3.2 Effects of Cannabinoids on Other Drugs

Although in vitro studies have suggested significant CYP-related drug interactions for Δ^9THC, 11-OH-THC and CBD, except for interactions with CYP1A1 and CYP1A2, the in vitro concentrations (measured in micromoles) associated with the interactions were significantly higher than the serum concentrations (measured in nanomoles) achieved after inhalation or oral dosing [82]. Marijuana tar extracts increased expression of CYP1A1 mRNA to a greater extent than tobacco extracts in a murine hepatoma (Hepa-1) cell line [83]. The induction of CYP1A1 expression was significantly reduced in Hep-1 mutants lacking AhR [83] and after knockdown of AhR expression by use of ARH small interfering RNAs [84], demonstrating that the induction was mediated by the AhR receptor. CBD inhibited CYP2C19-catalyzed omeprazole 5-hydrolase activity [85] and CYP2C9 *S*-warfarin 7-hydrolase and diclofenac 4′-hydrolase activity [86].

Theophylline and chlorpromazine are CYP1A2 substrates with minor metabolism by CYP3A4 [87, 88]. The effects of chronic tobacco and marijuana smoking alone and in combination were evaluated in subjects receiving a single 3–5 mg/kg oral dose of theophylline in orange juice [89]. Theophylline clearance was significantly faster in three males and four females who smoked both marijuana and tobacco (92.7 ± 25.3 mL/h/kg) than in five male and 19 female tobacco smokers (74.9 ± 30.8 mL/h/kg), and significantly faster in five male and two female frequent marijuana smokers (73.3 ± 20.7 mL/h/kg) than in 11 male and eight female non-smokers (51.8 ± 20.8 mL/h/kg). There were corresponding decreases in the average $t_{½}$ values, which were 4.3, 5.7 and 5.8 h in combination smokers, tobacco-only smokers and marijuana-only smokers, respectively, versus 8.1 h in non-smokers, with no effect on the volume of distribution (V_d). Regular use of marijuana or tobacco resulted in 61 and 31 % faster theophylline clearance in a group of 35 tobacco-smoking subjects and 14 marijuana-smoking subjects, respectively, than in 30 non-smoking subjects [90]. The effect on theophylline clearance occurs primarily with regular marijuana use (≥2 joints/week), with no effect of occasional use or lower exposure (<1 joint/week) [91].

In a population pharmacokinetic analysis of trough concentrations of chlorpromazine in 31 patients, there were five regular users of marijuana and 11 regular users of tobacco. The estimated clearance of chlorpromazine was 38, 50 and 107 % faster in regular users of tobacco, marijuana and the combination, respectively, than in non-users [92].

Antipyrine is metabolized by multiple CYP isozymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 [93]. The $t_{½}$ of antipyrine increased from a range of 6–13.8 h to 7.7–17.5 h in four of five subjects after oral intake of Δ^9THC 0.3 mg/kg twice daily for 7 days [94]. A similar increase in the average $t_{½}$ from 7.9 to 9.6 h was found in five of six male subjects receiving a single 10 mg/kg oral dose with placebo or Δ^9THC 10–30 mg in sesame oil orally every 4 h for 10–17 days [95]. An effect of Δ^9THC would be due to an increased V_d and/or decreased metabolism.

The effects of marijuana smoking on nicotine pharmacokinetics and the 3HC-to-cotinine ratio 270 min after a single dose of nicotine bitartrate containing 4 mg of nicotine base was evaluated in 68 African American healthy subjects, who were all *CYP2A6**1/*1 genotype [96]. There was no effect of marijuana use on CYP2A6 activity or nicotinamide pharmacokinetics when controlled for sex and tobacco use.

Indinavir and nelfinavir are metabolized by CYP3A4 [97]. Nelfinavir is also metabolized by CYP2C19 to an active metabolite that is subsequently eliminated by CYP3A4-dependent metabolism [98]. HIV-infected patients receiving either indinavir 800 mg every 8 h

($n = 28$) or nelfinavir 750 mg three times daily ($n = 34$) were randomized to receive either 3.95 % Δ^9THC marijuana cigarettes, dronabinol 2.5 mg capsules or placebo three times daily for 14 days [99]. There were no significant effects on the AUC from 0 to 8 h (AUC_8), C_{max} or minimum plasma concentration (C_{min}) of nelfinavir in comparison with baseline in patients receiving Δ^9THC or dronabinol. Δ^9THC significantly decreased the indinavir C_{max} by 14 %, with a trend towards a decrease (of 14.5 %) in the AUC_8. There was no effect of dronabinol on the pharmacokinetics of indinavir.

Clobazam is extensively metabolized by CYP3A4 and, to some extent, by CYP2C19 [100]. *N*-Desmethylclobazam, the primary metabolite, is pharmacologically active and is predominantly metabolized by CYP2C19. Six female and seven male children were receiving clobazam for the treatment of refractory epilepsy, and of the 13 children, 12 were also receiving one or two other concurrent AEDs [101]. CBD (Epidiolex; GW Pharmaceuticals) was initiated at 5 mg/kg/day, increased weekly by 5 mg/kg/day to a target of 25 mg/kg/day. The serum concentrations of clobazam and its active metabolite, *N*-desmethylclobazam, increased by 60 ± 80 and 500 ± 300 %, respectively, after use of CBD for 4 weeks, suggesting an inhibitory effect on CYP2C19 [101].

The effects of CBD on the pharmacokinetics of Δ^9THC were determined in a double-blind, placebo-controlled, crossover study in 12 male and 12 female subjects receiving a single oral dose of Δ^9THC 10 mg cannabis extract, Δ^9THC 10 mg + CBD 5.4 mg or placebo [102]. CBD significantly increased the AUC from 0 to 24 h (AUC_{24}) and the C_{max} of Δ^9THC by approximately 20 % and decreased the formation of 11-OH-THC. The effects of CBD were minor in comparison with the large intersubject variability in Δ^9THC and 11-OH-THC pharmacokinetics.

In conclusion, in vitro data and clinical data suggest that inhaled marijuana induces CYP1A2 to an extent similar to that observed with tobacco, with added effects when they are used in combination. There is also some limited evidence that inhaled marijuana may slightly induce CYP3A4, with no effect of orally administered synthetic Δ^9THC. The effect of CBD on clobazam suggests significant inhibition of CYP2C19, although the data are limited.

3.3 Effects of Other Drugs on Cannabinoids

The effects of multiple daily doses of rifampin 600 mg for 10 days, ketoconazole 400 mg for 6 days and omeprazole 40 mg for 6 days on the pharmacokinetics of Δ^9THC, 11-OH-THC and CBD after a single dose (4 sprays) of Sativex® oromucosal spray were determined in a randomized, crossover, parallel study in three groups of 12 male subjects [103]. Ketoconazole increased the C_{max} and AUC_{24} of Δ^9THC by 1.2- and 1.8-fold, respectively, increased the C_{max} and AUC_{24} of 11-OH-THC by 3.0- and 2.6-fold, respectively, and increased the C_{max} and AUC_{24} of CBD by 2- and 2-fold, respectively. Rifampin decreased the C_{max} and AUC_{24} of Δ^9THC by 40 and 20 %, respectively, decreased the C_{max} and AUC_{24} of 11-OH-THC by 85 and 87 %, respectively, and decreased the C_{max} and AUC_{24} of CBD by 50 and 60 %, respectively. There were no effects of omeprazole on the plasma concentrations of Δ^9THC, 11-OH-THC or CBD. The significant effects of rifampin and ketoconazole—which are a CYP3A4 inducer and a CYP3A4 inhibitor, respectively—suggest a major role of CYP3A4 in the metabolism of Δ^9THC, 11-OH-THC and CBD. Concurrent use of CYP3A4 inducers and inhibitors could result in significant drug interactions with cannabis products.

4 Smoking Cessation Products

4.1 Bupropion

Bupropion was initially approved for the treatment of major depression disorder, with subsequent approval for smoking cessation. Its mechanism of action in assistance with smoking cessation is unknown. Bupropion weakly inhibits uptake of dopamine and norepinephrine, which may mediate the anti-smoking properties.

4.1.1 Pharmacokinetics

Bupropion is almost completed absorbed, with t_{max} values of 1.5, 3 and 5 h for the immediate-release (IR), sustained-release (SR) and extended-release (ER) formulations, respectively [104]. Bupropion is administered as a racemic mixture and undergoes extensive first-pass metabolism to several active metabolites, with CYP2B6 being the primary isozyme involved [105]. The apparent oral clearance of (*S*)-bupropion is 3-fold faster than those of (*R*)- and (*R*,*S*)-bupropion, and hydroxylation of (*S*)-bupropion is used as an in vivo probe for CYP2B6 [106]. The primary active metabolite, hydroxyl-bupropion, is approximately 50 % as potent as bupropion. The C_{max} and AUC values of hydroxyl-bupropion are 4- to 7-fold and 10-fold higher, respectively, than those of bupropion with oral dosing. Threohydrobupropion and erythrohydrobupropion are also active metabolites formed by non-microsomal pathways and are approximately 20 % as potent as bupropion, with concentrations fivefold that of bupropion and equal to that of bupropion, respectively [107]. The $t_{½}$ values of bupropion, hydroxybupropion, erythrohydrobupopion and threohydrobupropion are approximately 21, 20, 33 and 37 h, respectively [107]. Bupropion is a substrate for breast

cancer resistant protein (BCRP) and P-glycoprotein (P-gp) transporters [108].

4.1.2 Effects of Bupropion on Other Drugs

Clinically, there are several reported interactions between bupropion and CYP2D6-metabolized drugs. In in vitro studies in human liver microsomes, bupropion (inhibitory constant [K_i] 21 μM) and hydroxybupropion (K_i 13.3 μM) are weak inhibitor of CYP2D6; however, erythrohydrobupropion (K_i 1.7 μM) and threohydrobupropion (K_i 5.4 μM) are more potent CYP2D6 inhibitors and theoretically are responsible for the drug–drug interactions [109]. The effects of steady-state bupropion SR 150 mg twice daily on the pharmacokinetics of a single 50 mg dose of desipramine were evaluated in CYP2D6 extensive metabolizers ($n = 15$) [107]. Bupropion decreased desipramine clearance and increased the C_{max}, AUC and $t_{½}$ by 2-, 5- and 2-fold, respectively. In a case report of a 64-year-old female on long-term imipramine 150–200 mg/day, imipramine and desipramine clearance decreased by 57 and 139 %, respectively when bupropion 225 mg/day was added [110]. In an open-label study in patients receiving fluoxetine ($n = 5$), paroxetine ($n = 4$) or venlafaxine ($n = 7$), bupropion SR 150 mg/day was added [111]. Venlafaxine plasma concentration increased 2.5-fold with addition of bupropion SR. There was no effect on the steady-state concentrations of fluoxetine or paroxetine. In a case report, a 22-year-old male, who was genotyped as *CYP2D6**1/*1 and phenotyped with dextromethorphan, converted to a poor-metabolizer phenotype when receiving bupropion for smoking cessation [112]. The case report was followed by a study evaluating the dextromethorphan-to-dextrorphan metabolic ratio in subjects who were phenotypically extensive metabolizers receiving bupropion SR 150 mg twice daily ($n = 13$) or placebo ($n = 8$) for 17 days [113]. The ratio increased significantly (0.012 ± 0.012 versus 0.418 ± 0.302) with concurrent bupropion treatment. Bupropion phenotypically converted six of the 13 subjects to poor CYP2D6 metabolizers.

4.1.3 Effects of Other Drugs on Bupropion

Chronic administration of carbamazepine, a broad-spectrum inducer of CYP and UGT isozymes, decreased the bupropion C_{max} and AUC_{24} by 87 and 90 %, respectively in 12 patients receiving a single 150 mg oral dose of bupropion [114]. There were significant increases in the C_{max} and AUC_{24} of hydroxybupropion—71 and 50 %, respectively. Valproate, an inhibitor of CYP2C9 and UGTs, did not alter bupropion plasma concentrations in five patients but increased the hydroxybupropion C_{max} by 56 % and AUC by 94 % by inhibiting the sequential metabolism of hydroxybupropion [114]. The effects of rifampin, a broad-spectrum CYP inducer, were determined in 18 healthy male subjects after a single dose of bupropion SR 150 mg before and after treatment with rifampin 600 mg/day for 7 days [115]. Rifampin increased bupropion clearance by 203 %, decreased the $t_{½}$ by 48 % and increased the hydroxybupropion C_{max} and AUC from 0 to 72 h (AUC_{72h}) by 39 and 43 %, respectively. The effects of genetic polymorphisms in the pregnane X receptor (PXR) and CYP2B6 on the induction of rifampin and bupropion hydroxylation were evaluated in 21 male and 14 female Korean subjects [116]. Subjects received a single oral dose of bupropion 150 mg before and after 7 days of rifampin 600 mg daily. The hydroxybupropion AUC from 0 to 36 h (AUC_{36h}) was significantly decreased in subjects with reduced-function PXR alleles and in *CYP2B6**6 carriers compared with non-carriers with and without rifampin treatment.

Both ritonavir and lopinavir are inhibitors of CYP3A, and ritonavir may also induce CYPC9 [117]. Four male and nine female healthy subjects received bupropion IR 150 mg alone after 3 days of ritonavir 200 mg three times daily and after 17 days of ritonavir in a randomized, crossover study [118]. Ritonavir increased the clearance of racemic, (*R*)- and (*S*)-bupropion by 1.2-fold after 3 days of treatment and by 1.4-, 1.7- and 1.5-fold, respectively, after 17 days of treatment. In a placebo-controlled crossover study of seven male healthy subjects receiving a single oral 75 mg dose of bupropion IR, there was no effect of ritonavir alone, administered as 200 mg twice daily for 2 days, on bupropion or hydroxybupropion pharmacokinetics [119]. The lower dose and shorter treatment (200 mg twice daily for 2 days, compared with 200 mg three times daily for 3 days) may explain the conflicting results of the two studies. The effects of 2-week treatment with lopinavir (400 mg)/ritonavir (100 mg) twice daily on the single-dose pharmacokinetics of bupropion SR 100 mg were determined in a crossover study in ten males and two females [120]. Lopinavir plus ritonavir decreased the bupropion C_{max} by 57 % and the AUC_{24} by 57 % and decreased the hydroxybupropion C_{max} and AUC_{24} by 31 and 50 %, respectively. There was no effect of bupropion on concentrations of lopinavir or ritonavir.

A randomized, two-phase study in ten male and three female healthy subjects evaluated the effects of a single dose of bupropion SR 150 mg administered with and without efavirenz 600 mg daily for 2 weeks [121]. Efavirenz decreased the AUC from 0 to 48 h (AUC_{48h}) and C_{max} of bupropion by 55 and 34 %, respectively, and increased the AUC ratio of hydroxybupropion to bupropion 2.3-fold, with no effect on the AUC of hydroxybupropion.

The pharmacokinetics of a single 150 mg oral dose of bupropion was evaluated alone and after pretreatment with

CYP2B6 inhibitors, clopidogrel 75 mg daily or ticlopidine 250 mg twice daily for 4 days each in 12 male subjects [122]. The bupropion AUC_{72h} was increased 60 and 85 % by clopidogrel and ticlopidine, respectively; the hydroxybupropion AUC_{72h} was decreased 52 and 84 % by clopidogrel and ticlopidine, respectively; and the hydroxybupropion-to-bupropion AUC ratio was increased 68 and 58 % by clopidogrel and ticlopidine, respectively. As there was no effect on the $t_{½}$ of bupropion, the interaction occurred during first-pass metabolism.

The effects of oral contraceptive (OC) and hormone replacement therapy (HRT) on CYP2B6 activity, using bupropion as a probe, were determined in a two-way crossover study in 12 healthy female subjects [123]. Subjects received a single 150 mg dose of bupropion SR without pretreatment, OC (ethinyl oestradiol 30 μg/desogestrel 150 μg) and HRT (oestradiol valerate 2 mg/levonorgestrel 250 μg) daily for 10 days each. HRT decreased the hydroxybupropion-to-bupropion AUC ratio by 49 %, which was due to a 47 % decrease in the AUC_{72h} of hydroxybupropion. The OC decreased the bupropion AUC_{72h} by 19 % and decreased the hydroxybupropion AUC_{72h} by 31 %, with no statistically significant difference in the hydroxybupropion-to-bupropion AUC ratio. Although there was only a modest effect on CYP2B6 with OC treatment, an increase in the bupropion dose may be needed for both OC and HRT users because of the significant decrease in the concentration of the active metabolite, hydroxybupropion.

The effects of St Johns' wort (SJW) on bupropion pharmacokinetics were studied in 18 healthy male Chinese subjects [124]. A single dose of bupropion was administered before and after a 14-day treatment with SJW given 325 mg three times daily. SJW decreased the bupropion AUC_{72h} by 17 %, with no effect on the $t_{½}$. Baicalin, a flavone glucuronide extract, increased the hydroxybupropion C_{max} and AUC_{72h} by 73 and 87 %, respectively, and increased the hydroxybupropion-to-bupropion AUC ratio by 63 % in 17 healthy male subjects receiving a single oral dose of bupropion 150 mg with and without a 14-day treatment with baicalin 500 mg three times daily [125]. There was no effect of baicalin on the oral clearance or $t_{½}$ of bupropion. Woohwangcheongsimwon, a suspension composed of 24 medicinal herbs commonly used in Korean and other East Asian countries, inhibited CYP2B6 [126], and *Ginkgo biloba* extract induced various hepatic CYPs, including CYP2B6, in vitro [127]; however, as has been observed with many herbal interactions, the in vitro data did not translate into clinically significant interactions. There was no effect of treatment with *Ginkgo biloba* extract 250 mg/day for 14 days on the single-dose pharmacokinetics of bupropion SR 150 mg in 14 healthy male subjects [128]. There was no effect of woohwangcheongsimwon suspension, administered for four doses, on the single-dose pharmacokinetics of bupropion SR 150 mg or hydroxybupropion in 15 male subjects [129].

In conclusion, the overall pharmacological effects of induction and inhibition of bupropion hydroxylation are dependent on the relative effects on bupropion and its major active metabolite, hydroxybupropion (Table 3). As hydroxybupropion concentrations are 7- to 10-fold higher after oral dosing, any significant decrease in hydroxybupropion could lead to reduced efficacy. In contrast, a significant increase could result in toxicity if dosages are not adjusted.

4.2 Varenicline

4.2.1 Pharmacokinetics

Varenicline, a synthetic analogue of cytisine, is an alpha-4-beta-2-nicotinic acetylcholine receptor partial agonist, which binds to nicotine receptors in the brain and is approved as an aid to smoking cessation. Varenicline is completely absorbed, with an average t_{max} of 3–4 h, and >90 % is eliminated unchanged in the urine, with a $t_{½}$ of 24–33 h after multiple dosing [130]. Active tubular secretion by human organic cation transporter 2 (hOCT2) contributes to the renal excretion and theoretically is a target for drug interactions [131].

4.2.2 Drug Interactions

In a randomized, placebo-controlled study in 24 healthy adult male and female smokers, there was no effect of varenicline 1 mg administered twice daily for 14 days on the pharmacokinetics of a single dose of warfarin 25 mg [132]. There was also no effect of varenicline on the pharmacokinetics of digoxin in 16 male and two female adult smokers receiving digoxin 0.2 mg daily with varenicline or placebo administered for 14 days in a randomized, crossover study [133]. In a randomized, crossover study in eight male and four female healthy adult smokers, cimetidine (a known inhibitor of hOCT2 [134]), administered in a dosage of 300 mg four times daily concurrently with a single 2 mg dose of varenicline, significantly decreased the renal clearance by 25 %, resulting in an increase in the AUC from 0 to 92 h (AUC_{92h}) of 29 % [131]. There was no effect on either metformin or varenicline pharmacokinetics when they were administered concurrently to 30 heathy adult smokers receiving metformin 500 mg twice daily and varenicline 1 mg twice daily for 7 days, in comparison with monotherapy [130].

Table 3 Bupropion drug interactions

	Proposed mechanism	Effect on concentrations	References
Bupropion as precipitant drug	CYP2D6 inhibition	↑ Desipramine	[107]
		↑ Imipramine	[107, 110]
		↑ Venlafaxine	[111]
		↑ Dextromethorphan	[111]
Bupropion as object drug			
Carbamazepine	CYP induction	↓ C_{max} and ↓ AUC of bupropion	[114]
		↑ C_{max} and ↑ AUC of hydroxybupropion	
Valproate	UGT inhibition	↔ C_{max} and ↔ AUC of bupropion	[115]
		↑ C_{max} and ↑ AUC of hydroxybupropion	
Rifampin	CYP induction	↓ C_{max} and ↓ AUC of bupropion	[116]
		↑ C_{max} and ↑ AUC of hydroxybupropion	
Ritonavir	CYP induction	↓ C_{max} and ↓ AUC of bupropion	[118]
		↔ C_{max} and ↓ AUC of hydroxybupropion	
	No effect	↔ C_{max} and ↔ AUC of bupropion	[119]
		↔ C_{max} and ↔ AUC of hydroxybupropion	
Ritonavir/lopinavir	CYP induction	↓ C_{max} and ↓ AUC of bupropion	[120]
		↓ C_{max} and ↓ AUC of hydroxybupropion	
Efavirenz	CYP induction	↓ C_{max} and ↓ AUC of bupropion	[121]
		↔ C_{max} and ↓ AUC of hydroxybupropion	
Clopidogrel	CYP2B6 inhibition	↑ C_{max} and ↑ AUC of bupropion	[122]
Ticlopidine		↓ C_{max} and ↓ AUC of hydroxybupropion	
Oral contraceptive therapy	CYP2B6 inhibition	↓ C_{max} and ↓ AUC of bupropion	[122]
		↓ C_{max} and ↓ AUC of hydroxybupropion	
Hormone replacement therapy	CYP2B6	↔ C_{max} and ↓ AUC of bupropion	[122]
		↓ C_{max} and ↓ AUC of hydroxybupropion	
St John's wort	CYP induction	↔ C_{max} and ↓ AUC of bupropion	[124]
		↔ C_{max} and ↔ AUC of hydroxybupropion	
Baicalin	CYP induction	↔ C_{max} and ↓ AUC of bupropion	[125]
		↑ C_{max} and ↑ AUC of hydroxybupropion	

AUC area under the plasma concentration–time curve, C_{max} maximum plasma drug concentration, *CYP* cytochrome P450, *UGT* uridine diphosphate glucuronosyltransferase

4.3 Cytisine

Cytisine, a plant alkaloid and a partial agonist of α4β2 nicotinic receptors, is widely used in Eastern and Central European countries as a smoking cessation agent [135, 136]. The pharmacokinetics of a single oral dose of cytisine 3 mg was determined in seven healthy male subjects who were current cigarette smokers [137]. Peak concentrations occurred 2 h after oral administration, with an average $t_{½}$ of 4.8 h. Only unchanged cytisine was detected in the urine. The role of active renal tubular secretion in renal excretion of cytisine has not been determined. Cytisine is not a substrate of P-gp or BCRP efflux transporters [138]. In rats, the low brain exposure to cytisine compared with varenicline, even with the small differences in their molecular properties, suggests that cytisine is a substrate for other non-P-gp or BCRP efflux transporters [138]. There have been no published drug interaction studies.

4.4 Other Treatment Options for Smoking Cessation

Clonidine and nortriptyline are considered second-line therapies for smoking cessation because of the limited number of available randomized, controlled trials and lack of data to demonstrate their long-term efficacy [139, 140]. Clonidine is a centrally active antihypertensive agent, which has also been found to have analgesic and antisecretory effects in the gastrointestinal tract. About half of the administered dose is excreted renally unchanged. There

is no established evidence demonstrating a pharmacokinetic or pharmacodynamic interaction between clonidine and smoking. Nortriptyline is a tricyclic antidepressant. The primary enzymes involved in its metabolism include CYP1A2, 2D6 and 2C19, with CYP3A4 being a minor metabolic pathway [141, 142]. Therefore, smoking is expected to reduce the clinical efficacy of nortriptyline because of CYP1A2 induction, whereas in a patient who has been receiving chronic nortriptyline therapy, dose reduction will likely be necessary when the patient is undergoing smoking cessation, to prevent adverse drug events.

5 Conclusion

Both tobacco smoking and marijuana smoking result in significant upregulation of CYP1A1 and 1A2, which alters the pharmacokinetics of drugs metabolized by these enzymes (Table 1). On the basis of limited studies, the induction potential of chronic marijuana use appears to be approximately equal to or greater than that of tobacco, with the combination resulting in the greatest CYP1A2 induction, suggesting that PAHs are the primary inducing agents for both. The interaction potential of nicotine itself is less understood, with limited drug interactions involving CYP2A6 inhibition or induction. Although CYP2C19 is primarily responsible for formation of the active metabolite of Δ^9THC, 11-OH-THC, the significant effects of CYP3A4 inducers and inhibitors on the pharmacokinetics of Δ^9THC, 11-OH-THC and CBD after administration of Δ^9THC and CBD oromucosal spray suggest that CYP3A4 is a major enzyme responsible for the metabolism of Δ^9THC and CBD. Limited data also suggest that CBD may significantly inhibit CYP2C19. CYP2B6 inducers and inhibitors significantly alter the pharmacokinetics of bupropion. However, the clinical significance of the interactions is complex because of the presence of several active metabolites. The pharmacodynamic effects of each interaction needs to be determined separately. Smoking cessation results in rapid downregulation of CYP1A2 enzyme activity, which may require dose adjustment of some chronic medications to prevent toxicity. With the increasing use of marijuana and cannabis products medically and recreationally, future clinical studies are needed in order to clarify the drug interaction potential.

Compliance with Ethical Standards

No sources of funding were used in the preparation of this review. Gail D. Anderson and Lingtak-Neander Chan have no conflicts of interest that are directly relevant to the content of this review.

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