

WHO Expert Committee on Drug Dependence Pre-Review

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Cannabis plant and resin

Section 2: Pharmacology



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1. General Pharmacology

Studies included in this pharmacology pre-review are those involving:

- Cannabis as defined by the International Drug Control Conventions as "the flowering tops of the cannabis plant from which the resin has not been extracted." The term "cannabis" generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which is defined as "the separated resin, whether crude or purified, obtained from the cannabis plant". It is normally in solid form and is sometimes known as hashish.

Most of the studies covered herein involve cannabis delivered via smoking. While the flowering tops of the cannabis plant may be vaped, this practice is relatively new and scientific literature on its distinct pharmacological effects (vs. smoking) are not available. Vaping cannabis-derived oils will be described in the extracts pre-review. Similarly, the initial step in creation of cannabis edibles typically involves extracting and concentrating cannabinoids contained in the cannabis plant. Hence, the literature on these products will also be covered in the cannabis extracts pre-review.

1.1 Routes of administration and dosage

To date, over 500 naturally occurring compounds have been identified in the cannabis plant, including cannabinoids (> 100 chemicals unique to the plant), terpenoids, and alkaloids.¹⁻³ Earlier research identified Δ^9 -tetrahydrocannabinol (Δ^9 -THC) as the primary psychoactive constituent in cannabis,⁴ resulting in special emphasis being placed on delineation of the pharmacology of this constituent in subsequent research. In the plant, Δ^9 -THC is present primarily in its acid form, Δ^9 -THCA; however, it is rapidly decarboxylated to Δ^9 -THC upon heating or burning, as occurs during smoking or in the extraction process. Concentrations of Δ^9 -THC contained in cannabis vary across strains and across the plant itself, with resin (i.e., hashish) and unfertilized female flowers (i.e., sinsemilla) having high concentrations compared to other parts such as the leaf. In addition, significant increases in Δ^9 -THC concentrations in seized or purchased cannabis have been documented over recent years in several countries, including the U.S. and U.K.^{5, 6} For example, average Δ^9 -THC concentration in cannabis samples in the U.S. in 1995 was ~4%; by 2014, average

Δ^9 -THC concentration had increased to ~12%,⁵ with some samples containing over 20% Δ^9 -THC.⁵⁻⁷ Concentrated extracts contained even higher concentrations of Δ^9 -THC (average ~ 68%).⁷ Concomitant decreases in cannabidiol (CBD) concentration have also been noted, with negligible CBD in sinsemilla and an average of 2.3% CBD in cannabis resin.^{5,6} Selective breeding and greater use of plant parts with higher Δ^9 -THC concentrations (e.g., sinsemilla), both driven by consumer demand for stronger cannabis, may have contributed to this increased availability of high- Δ^9 -THC/low-CBD cannabis.⁵⁻⁷ Hence, “dosage” for cannabis and its resin usually refers to Δ^9 -THC dose/concentration rather than to amounts of the other cannabinoid and non-cannabinoid constituents contained in the cannabis plant.

Cannabis and cannabis resin (i.e., hashish) are typically administered via inhalation after combustion (i.e., smoking). Because each inhalation of smoke from a cannabis cigarette or other delivery device (e.g., pipe, vaporizer) delivers a proportion of the chemicals contained in the cannabis, Δ^9 -THC concentration is an important consideration in determination of how much Δ^9 -THC enters the body through the lungs. Other factors that affect amount of Δ^9 -THC that ultimately is absorbed include topography of smoking behavior (e.g., puff volume and duration, number of puffs), individual differences in lung physiology, and amount lost to side stream smoke or pyrolysis.⁸⁻¹² Desired Δ^9 -THC dosage is self-determined by the user and may change over time due to the development of tolerance.

1.2 Pharmacokinetics

In humans, the predominant route of administration of cannabis or cannabis resin is inhalation after combustion (i.e., smoking). For this reason, discussion of the pharmacokinetics of cannabis and its resin will concentrate on inhalation as a route of administration. In the plant, Δ^9 -THC is present primarily in its acid form, Δ^9 -THCA, which is rapidly decarboxylated to Δ^9 -THC upon heating or burning, as occurs during smoking or in the extraction process. Hence, the bulk of the extant research on cannabis pharmacokinetics has focused on Δ^9 -THC. This section will begin with a discussion of the pharmacokinetics of Δ^9 -THC delivered via smoking cannabis followed by a brief review of the pharmacokinetics of CBD and possible metabolic interactions of Δ^9 -THC and CBD. Two excellent comprehensive reviews served as the basis for much of this section.^{11,13}

1.2.1 Δ^9 -Tetrahydrocannabinol

Absorption of Δ^9 -THC in smoked cannabis is rapid and measurable levels are observed in plasma seconds after the first puff.^{11, 14} While peak plasma levels typically occur in 3-10 minutes after smoking, peak “highs” do not occur until 20-30 minutes after smoking,¹¹ although others have reported an earlier peak.¹⁴ Because Δ^9 -THC concentrations in the plasma may have already started to fall before maximal effect, plasma levels are not the best predictor of intoxication.¹⁵ Bioavailability of Δ^9 -THC after cannabis smoking ranges from 10 to 56%, with several factors contributing to the variability, including dose, smoking efficiency/topography, history of cannabis use, and individual differences in physiology.^{11, 13} In addition, approximately 30% of the Δ^9 -THC concentration in the plant material may be destroyed by pyrolysis and an additional variable amount may be lost in side stream smoke.¹¹

Due to its high lipophilicity, Δ^9 -THC is highly bound to plasma proteins and is readily distributed to highly vascularized tissues (e.g., liver, heart) after absorption from the lung.¹¹ Although smoking cannabis avoids the significant first-pass metabolism associated with orally administered Δ^9 -THC, plasma-protein binding and rapid distribution to tissues contribute to rapidly falling plasma levels of Δ^9 -THC following cannabis smoking, even as pharmacological effects (including centrally mediated subjective effects) continue.^{11, 13, 16} In experienced cannabis smokers, cannabis-induced subjective effects (e.g., “good drug effect,” “high,” “stoned”) have been found to be stronger during the distribution and elimination phases than during absorption.¹⁷ These prolonged cannabinoid behavioral effects, which occur despite reduced Δ^9 -THC plasma levels, may result from slow elimination of Δ^9 -THC from the brain, coupled with the cannabimimetic effects of its highly penetrant and equipotent active metabolite, 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH- Δ^9 -THC).^{11, 18} Body fat also serves as a storage reservoir for Δ^9 -THC and its metabolites, as Δ^9 -THC is eliminated from fat tissues even more slowly than from brain.¹¹

Metabolism of Δ^9 -THC contained in cannabis smoke occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified.¹¹ Hydroxylation of the C-11 site to form 11-OH- Δ^9 -THC is the initial step of the biotransformation in most species, including humans.^{19, 20} This major metabolite is psychoactive, as indicated by its cannabimimetic effects in mice,²¹ its substitution for Δ^9 -THC in rat drug discrimination,²² and its similar psychological effects in men.^{18, 23} Data from early studies suggested that 11-OH- Δ^9 -THC may have greater brain penetrance than Δ^9 -THC.¹¹ However, unlike with orally administered Δ^9 -THC, cannabis smoking results in low brain levels of 11-OH- Δ^9 -THC (vs Δ^9 -THC).¹³ Although hydroxylation of Δ^9 -THC at C-11 to form 11-OH- Δ^9 -THC is most common, hydroxylation may also occur at C-8, resulting in formation of 8-OH-THC and 8-OH-THC in rodents¹⁹ and 8-OH-THC in human hepatic microsomes.²⁴ I.v.

administration of the epimers to a small sample of men revealed that both epimers were active, but potency of the δ^9 -epimer exceeded that of the δ^8 -epimer.²⁵ The primary CYP isoenzymes that catalyze the hydroxylation reactions are CYP2C9 and CYP3A4.^{24, 26} A secondary metabolite, 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (11-COOH- Δ^9 -THC or THC-COOH), is formed through oxidation of 11-OH- Δ^9 -THC.²⁷ THC-COOH lacks cannabimimetic effects and is further metabolized to its glucuronide conjugate, which is water soluble and excreted in urine.^{13, 26} Due to its extensive metabolism, relatively little Δ^9 -THC is eliminated from the body unchanged. Δ^9 -THC is excreted primarily in the feces (65-80%) and in the urine (20-35%).¹¹

1.2.2 *Cannabidiol*

The pharmacokinetics of cannabidiol (CBD) and other minor phytocannabinoids contained in the cannabis plant, including cannabitol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV), following smoked cannabis resemble that observed with Δ^9 -THC.¹¹ Absorption of smoked CBD is rapid, with bioavailability averaging about 31%. As seen with Δ^9 -THC, primary metabolism occurs via oxidation at C9 and at the side chain.¹³ However, unlike with Δ^9 -THC, a high percentage of CBD is eliminated unchanged in the feces.^{11, 13}

Animal work has suggested that CBD may hinder or delay Δ^9 -THC metabolism through competition for or inactivation of CYP P450 enzymes,^{28, 29} resulting in enhancement of Δ^9 -THC's in vivo effects.³⁰ However, this research generally used higher concentrations of CBD (in relation to Δ^9 -THC concentration) than are typically present in most cannabis strains. In contrast, lower CBD concentrations failed to accentuate Δ^9 -THC's effects in rodents.³⁰ The degree to which a similar metabolic interaction occurs in humans is uncertain, with extant evidence suggesting that it does not at the ratios of Δ^9 -THC:CBD normally seen in cannabis.^{11, 31-33}

1.3 Pharmacodynamics

To date, over 500 naturally occurring compounds have been identified in cannabis, including cannabinoids (> 100 chemicals unique to the plant), terpenoids, and alkaloids.^{1-3, 34} However, except for Δ^9 -THC, most of these other compounds are present in the plant in relatively small quantities. The degree to which they may contribute to the array of pharmacological and behavioral effects produced by cannabis is largely unknown. Hence, the discussion below focuses primarily on the pharmacodynamics of Δ^9 -THC followed by a summary of the possible contribution of other constituents to cannabis' effects.

1.3.1 Δ^9 -Tetrahydrocannabinol

When administered to animals, Δ^9 -THC produces characteristic profile of pharmacological effects which includes a tetrad of effects in mice and rats (locomotor suppression, antinociception, hypothermia and ring/bar immobility), discriminative stimulus effects (rats, mice, pigeons, rhesus monkeys), reinforcing effects (squirrel monkeys), and static ataxia (dogs).³⁵⁻³⁷ These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.³⁸ Within this endocannabinoid system, two cannabinoid receptors, CB₁ and CB₂, have been identified.^{39, 40} While CB₁ receptors are widespread and abundant in the brain and periphery, CB₂ receptors are confined primarily to the periphery,⁴¹ although recent evidence suggests that CB₂ receptors may be present in the brain under certain conditions.⁴² Δ^9 -THC is a partial agonist at both types of cannabinoid receptors, at approximately equal affinities ($K_i = 41$ and 36 nM for CB₁ and CB₂ receptors, respectively).⁴³ Further, the affinities of cannabis smoke and pure Δ^9 -THC for the CB₁ receptor are similar for cannabis containing an equivalent amount of Δ^9 -THC,⁴⁴ emphasizing the degree to which Δ^9 -THC is predominant in the pharmacology of smoked cannabis. Δ^9 -THC's psychoactivity is mediated via activation of CB₁ receptors in the brain in a manner resembling activation by their endogenous ligands (e.g., anandamide and 2-arachidonoylglycerol). For example, research has shown that the discriminative stimulus effects of Δ^9 -THC in animals were reversed by pre-injection with rimonabant, a selective CB₁ receptor antagonist, but not by injection with SR144528, selective CB₂ receptor antagonist.⁴⁵ Similarly, the reinforcing effects of THC in squirrel monkeys were reversed by rimonabant,⁴⁶ as were its antinociceptive, hypothermic and cataleptic effects in rodents⁴⁷ and its induction of static ataxia in dogs.³⁷ Antagonists of other major neurotransmitter systems (e.g., dopamine, acetylcholine, norepinephrine, mu opioid) did not alter the discriminative stimulus effects of Δ^9 -THC in rats.²² Consistent with these in vivo results, Δ^9 -THC does not have significant affinity for non-cannabinoid receptors of these major systems.⁴⁸ In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64-2.78% Δ^9 -THC,^{49, 50} suggesting that the antagonism results from preclinical Δ^9 -THC antagonism experiments are translational.

While Δ^9 -THC produces its characteristic pharmacological effects via activation of CB₁ and CB₂ receptors, the brain's endocannabinoid system has extensive interconnections with a variety of other neurotransmitter systems, including dopamine, GABA, glutamate, opioid, and norepinephrine.⁵¹⁻⁵⁴ Hence, activation of this system through exogenous administration of Δ^9 -THC may have widespread indirect effects on modulatory endocannabinoid-induced regulation of these other neurotransmitters.⁵⁵ Of note, similar to the action of many other drugs of abuse, acute administration of Δ^9 -THC induces dopamine efflux in

reward-related brain areas.⁵² In contrast, withdrawal from Δ^9 -THC after chronic administration is associated with decreased activation of dopamine neurons.^{56, 57}

1.3.2 *Cannabidiol and Other Minor Cannabinoids*

In addition to cannabidiol (CBD), minor phytocannabinoids in cannabis include cannabinol (CBN), cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), and cannabichromene (CBC).³⁴ Some of these phytocannabinoids bind to the CB₁ receptor with high affinity: CBN (K_i=13 nM) and THCA (K_i=23.5 nM); others had low or negligible affinity: CBG (K_i=897 nM) and CBDV (K_i=14,711 nM).⁵⁸ These minor phytocannabinoids may affect the pharmacology of cannabis via two basic mechanisms: (1) the pure constituent may have pharmacological effects and/or (2) the constituent may interact with Δ^9 -THC and alter its effects (e.g., “entourage” effect).^{2, 59} While research has examined the pharmacological effects of some of these phytocannabinoids (especially CBD), much of this research has focused on potential therapeutic effects and has utilized doses of a single constituent that would far exceed its concentration in a cannabis cigarette.^{2, 60-64} Hence, with exception of CBD (discussed in the extracts pre-review),⁶⁵ this research with single constituents does not provide clear information about the pharmacodynamics of cannabis as it is used in humans. Similarly, research that has used smoked cannabis (which presumably contains all naturally occurring chemicals in the plant) has not offered clear support for the “entourage” hypothesis, with a possible exception of pharmacokinetic interaction between CBD and Δ^9 -THC.

2. Dependence Potential

2.1.1 Animal Studies

Three labs have investigated the dependence potential of smoked cannabis in animals. In mice, daily ~5-min exposure to cannabis smoke (3.46% Δ^9 -THC; 0.05-0.18% CBD, CBN, CBG, and THCV) for 5 days resulted in rimonabant-precipitated withdrawal characterized by an increase in paw tremors.⁶⁶ Estimated ED₅₀ for Δ^9 -THC in the smoked cannabis was 3.6 mg/kg whereas the ED₅₀ for i.v. Δ^9 -THC was 4.1 mg/kg. Administration of i.v. Δ^9 -THC reversed withdrawal-induced paw tremors; however, smoked cannabis did not. Serum Δ^9 -THC levels after exposure to the smoke of cannabis containing 100 or 200 mg of Δ^9 -THC was comparable to those obtained with 3 mg/kg Δ^9 -THC i.v., but concentrations of Δ^9 -THC in the brain with smoked cannabis bore greater similarity to those obtained with 1 mg/kg Δ^9 -THC i.v. Whereas serum Δ^9 -THC concentrations dropped more rapidly after i.v. administration than after smoking, brain concentrations decreased in parallel.

In rats, daily 1-hour exposure to cannabis smoke (5.7% Δ^9 -THC) five times a week for eight weeks also induced dependence.⁶⁷ As with mice, rimonabant administration precipitated withdrawal, which was characterized by large increases in grooming and eye blinks as well as smaller increases in ptosis, wet dog shakes, and forepaw flutters. While these results showed that rimonabant-precipitated withdrawal occurred after daily exposure to Δ^9 -THC-containing cannabis smoke in rodents, the potential for a similar regimen of smoke exposure to induce spontaneous withdrawal after abrupt cessation was not examined in these rodent studies.

In rhesus monkeys, examination of the dependence potential of smoked cannabis (2.6% Δ^9 -THC) occurred prior to rimonabant availability; hence, only spontaneous withdrawal could be evaluated. Two exposure regimens were used, with some monkeys receiving exposure to the smoke of one cannabis cigarette per day seven days a week while others were exposed to the same Δ^9 -THC amount for two days per week. In each case, exposure was continued for one year. Evaluation during the active exposure phase of the study revealed increases in progressive ratio responding for food reinforcement in control monkeys, which were not observed in cannabis-exposed monkeys.⁶⁸ This response suppression lasted for 2-3 months after termination of cannabis exposure before recovery to control levels. Abrupt cessation of smoke exposure was associated with disruption of responding in progressive ratio and conditioned position responding in both control and cannabis-exposed groups, suggesting that it was related to the interruption of daily routine rather than to withdrawal from cannabis *per se*.⁶⁸ Seven months after the last exposure to cannabis

smoke, a subset of monkeys was sacrificed and the caudate and hypothalamus of each monkey was removed for analysis. Results revealed no long-term changes in either monoamine concentrations⁶⁹ or CB₁ receptor densities.⁷⁰ Although this multi-dimensional study does not offer support for the hypothesis that smoked cannabis has the potential to produce dependence in monkeys, the percentage of Δ^9 -THC contained in the cannabis used in the study (2.6%) was several-fold lower than the concentrations of Δ^9 -THC in cannabis that is now available (e.g., ~12% Δ^9 -THC in samples seized in 2014 in the United States).⁵

2.1.2 Human Studies

Cannabis dependence is characterized by the development of withdrawal symptoms upon abstinence from regular use. Multiple lines of evidence have converged to confirm and characterize a cannabis withdrawal syndrome. In recognition of this evidence, the fifth edition of the *Diagnostic and Statistical Manual*, used for diagnosis of mental illness and substance abuse disorders in the U.S., outlines criteria for the syndrome and includes a specific diagnostic code for “Cannabis Use Disorder.”⁷¹ The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) also recognizes cannabis dependence, but does not list specific withdrawal criteria.⁷² The body of evidence supporting these classifications encompasses laboratory studies in inpatients, ecological momentary assessment and self-report investigations in outpatients, and structured online surveys.⁷³⁻⁸¹

Estimated percentage of regular cannabis users who have experienced at least one episode of cannabis withdrawal during abstinence (e.g., when trying to quit) range from 16 to 33%, dependent upon the sample used for study.^{73, 82} Because worldwide use of cannabis is more extensive than any other illicit substance, with estimates ranging from 2.7 to 4.9%,⁸³ the absolute number of people across the globe who have experienced cannabis withdrawal is quite large. However, rates of dependence are not equal in all countries. Rather, they exhibit geographical diversity, which is related to economic and cultural factors as well as to variability in the availability of specific types of cannabis.^{77, 84} For example, a vast array of cannabis products with various Δ^9 -THC concentrations can be purchased in Colorado, the first U.S. state to legalize non-medicinal use of cannabis. In contrast, availability in Uruguay is restricted to five strains.⁸⁴ Rank order prevalence of cannabis dependence is highest in Australasia > North America > Western Europe > Central Asia and least in Southern Latin America.⁷⁷

The availability of high potency cannabis is associated with increased prevalence of cannabis dependence,⁷⁷ with cannabis potency being assessed in terms of Δ^9 -THC concentration. Chemotypes of cannabis include high potency plants that are usually cultivated indoors under carefully controlled conditions (> 15% Δ^9 -THC); low potency plants that often are grown outdoors (~ 9% Δ^9 -THC); and compressed blocks of plant

matter (~ 5% Δ^9 -THC plus CBD).⁸⁴ While considerable variability in Δ^9 -THC concentrations has been observed across chemotypes, this classification scheme is helpful because it emphasizes the role that Δ^9 -THC plays in the development of dependence. Interestingly, chronic smoking of cannabis over a period of years has been associated with CB₁ receptor downregulation in humans,⁸⁵ an effect that also occurs in rodents who have been administered repeated doses of Δ^9 -THC or other cannabinoid agonist.⁸⁶

In humans, onset of withdrawal typically occurs within 24 to 48 hours of abstinence following a period of regular use. The sequelae of physical and psychological symptoms comprising the withdrawal syndrome may include mood changes, irritability, increased anger, anxiety, craving, restlessness, sleep impairment, stomach pain, and decreased appetite, with most individuals reporting four or more symptoms.^{73-75, 78, 82} Psychological symptoms predominate, with peak intensity usually 2 to 6 days after last use. Similar to withdrawal from other drugs of abuse (e.g., nicotine), maximal discomfort lasts 2 to 3 weeks with gradual return to baseline,⁷⁶ although disruption of sleep may linger.⁸¹ Partial recovery of CB₁ receptor functioning occurs over a similar period of time, suggesting that cannabis dependence is related to Δ^9 -THC-induced changes in the endocannabinoid system.⁸⁷ Withdrawal symptoms are alleviated by re-administration of oral Δ^9 -THC⁸⁸ and increased self-reported severity of symptoms is associated with return to cannabis smoking (i.e., self-medication).⁸⁹ While dependence may develop with regular use of cannabis of low potency,⁷⁸ regular use of high potency cannabis is associated with enhanced severity of withdrawal symptoms as well as with increased risk memory impairment and paranoia.⁸⁴ Nevertheless, users report that high potency cannabis provides the “best high” and is most preferred.⁸⁴

3. Abuse Potential

3.1.1 *Animal Studies*

Because of the technical challenges which accompany exposure of animals to smoke from combustion of cannabis or its resin, only a few behavioral pharmacologists have pursued investigation of the abuse potential of cannabis in animals. Rather, most have used systemic injection of Δ^9 -THC as a proxy for cannabis. However, this approach ignores at least two factors that may be relevant to the translational implications of this preclinical research for the abuse potential of cannabis: (1) in humans, cannabis or its resin is typically self-administered via smoking rather than by injection and differences across route of administration could conceivably affect abuse potential; and (2) in addition to Δ^9 -THC, cannabis contains numerous other cannabinoid and non-cannabinoid chemicals that may alter or add to Δ^9 -THC's behavioral effects.¹

A handful of studies have attempted to overcome these challenges through using inhalation exposure to combusted cannabis with defined amounts of Δ^9 -THC and other cannabinoids, such as CBD, CBN, CBG, and THCV. Whereas an older study demonstrated that exposure to smoke from combustion of cannabis containing 2.1% Δ^9 -THC (and 0.2% CBN and CBD) produced immediate and short-acting (~ 3 minutes) hyperactivity followed by longer duration (> 1 hour) hypoactivity,⁹⁰ more recent studies have used cannabis with higher (5.19-5.7%) concentrations of Δ^9 -THC, but with similarly low concentrations of other cannabinoid constituents. In rats, acute exposure to Δ^9 -THC-containing cannabis smoke increased locomotor activity followed by decreases at later time points.⁶⁷ Decreased rearing also was observed, an effect that was reversible by the CB₁ receptor antagonist rimonabant. In mice, nose-only inhalation of smoke from cannabis with these higher Δ^9 -THC concentrations produced characteristic cannabinoid effects of antinociception, catalepsy, and hypothermia that were similar in magnitude to those induced by i.v. Δ^9 -THC.^{30, 91, 92} Locomotor suppression effects were also observed; however, these effects were obscured by comparable effects seen in mice exposed to placebo smoke. All observed effects in the tetrad battery (regardless of route of Δ^9 -THC administration) were attenuated by pre-injection with rimonabant, suggesting that they were CB₁ receptor-mediated. Further, potencies for i.v. Δ^9 -THC were similar to those obtained with smoked cannabis containing comparable quantities of Δ^9 -THC. Based on the accumulated data, the authors concluded that the characteristic behavioral effects of Δ^9 -THC in the tetrad battery in mice were not altered by the low concentrations of CBD and other cannabinoids normally present in cannabis;^{30, 92} i.e., Δ^9 -THC alone was responsible for these effects. In contrast, when a higher concentration of CBD (30 mg/kg) was administered i.v., Δ^9 -THC concentrations in the brain and serum were increased and

its antinociceptive effects were enhanced.³⁰ These results are consistent with previous data showing that higher concentrations of CBD inhibit Δ^9 -THC metabolism via cytochrome P450 mechanisms.²⁸ Further, these increases in Δ^9 -THC concentrations in brain and serum were not observed after exposure to Δ^9 -THC-containing cannabis smoke,³⁰ a route of administration that would avoid first-pass metabolism.

3.1.2 Human Studies

Although development of robust i.v. Δ^9 -THC self-administration in animal models has been relatively elusive until recently, cannabis is readily self-administered by humans despite possible negative legal consequences.⁹³ In the 2015 World Drug Report, estimates of global prevalence of cannabis use ranged from 2.7 to 4.9% and the trend was towards increases.⁸³ The reinforcing effects of smoked cannabis also have been demonstrated in a number of laboratory-based self-administration procedures. Smoked cannabis is readily self-administered by experienced users.⁹⁴ In these studies, participants chose to smoke cannabis cigarettes (Δ^9 -THC content ranging from 1.8 to 5.8%) rather than placebo cigarettes in choice procedures⁹⁵⁻⁹⁷ and preferred higher doses over lower doses within this range.^{98, 99} When given the opportunity, most subjects were willing to work to smoke cannabis.^{98, 100} However, when given a choice between smoking cannabis (1.8 or 3.9% Δ^9 -THC) or performing a computer task for money, the degree to which subjects preferred cannabis or money depended upon the amount of work required to earn the money. When the performance criteria for money were high, subjects chose to smoke cannabis, but when the criteria were low, their choice switched to money.^{98, 101} These results suggest that preference for cannabis is malleable dependent upon its availability and response cost of alternative reinforcers.

A drug discrimination model has also been employed to examine the subjective effects of smoked cannabis in humans. Chait and colleagues¹⁰² found that study participants readily learned to discriminate cannabis smoke (2.7% Δ^9 -THC) from placebo cigarette smoke, with high (~90%) accuracy. Cannabimimetic discriminative stimulus effects were characterized by rapid onset (often after as little as two puffs), were dependent upon Δ^9 -THC concentration, and lasted up to 120 minutes. Self-reported subjective effects associated with smoked cannabis in laboratory studies include dose-dependent increases in ratings of “drug effect,” “high” or “stoned.”^{96, 100, 103, 104} Similar effects were produced by Δ^9 -THC alone when administered orally or when smoked.^{100, 103, 105} These results suggest that the cannabis constituent responsible for the plant’s reinforcing effects is Δ^9 -THC. This hypothesis receives further support from the finding that orally administered doses of CBD (200-800 mg) did not alter self-administration of smoked cannabis or associated increases in ratings of “high” or “stoned.”⁹⁶ Similarly, the effects of smoked cannabis on subjective, physiological, and performance measures varied with the concentration of Δ^9 -THC, but not with

concentration of the minor constituents CBD and cannabichromene (CBC).¹⁰⁶ Rimonabant reversal of intoxication induced by cannabis smoking has been reported in one study,⁴⁹ but not in another,⁵⁰ both conducted in the same laboratory.

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