WHO Expert Committee on Drug Dependence Pre-Review

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Delta-9-tetrahydrocannabinol

Section 2: Pharmacology

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1. **General Pharmacology**

The primary psychoactive constituent occurring naturally in the *Cannabis sativa* plant is Δ⁹-tetrahydrocannabinol (Δ⁹-THC), which may also be synthesized for medical (e.g., dronabinol) or research use. Stereochemical variants of Δ⁹-THC include the following:

- (−)-trans-Δ⁹-THC (also known as dronabinol)
- (+)-trans-Δ⁹-THC
- (−)-cis-Δ⁹-THC
- (+)-cis-Δ⁹-THC

With exception of research designed to examine the effects of stereoisomers specifically, many articles did not specify the form of Δ⁹-THC that was used in the study. In the pharmacology pre-review sections, the stereoisomer name is provided when it was mentioned. When the article refers to use of “Δ⁹-THC” and does not specify a stereoisomer, Δ⁹-THC is used in the text. However, (−)-trans-Δ⁹-THC is the most likely referent in these papers for several reasons: (1) it is the naturally occurring optical isomer present in the plant; (2) this stereoisomer is provided by the United States National Institute on Drug Abuse (NIDA) Drug Supply Program to researchers in the U.S. who request “Δ⁹-THC” for their preclinical research; and (3) cannabimimetic psychoactivity is selective for this (−)-isomer as compared to the (+)-isomers. Studies that examined the effects of specific stereochemical variants are mentioned at the end of each pharmacology section.

1.1 **Routes of administration and dosage**

Δ⁹-THC is highly lipophilic and is readily absorbed and distributed to the brain and other organs following many routes of administration in animals, including intraperitoneal (i.p.), oral (p.o.), intramuscular (i.m.), intravenous (i.v.), and inhalation. In humans, the predominant route of administration of Δ⁹-THC that is not contained in or extracted from the cannabis plant (covered in separate pre-reviews) is oral (i.e., dronabinol). Therapeutic indications for dronabinol (Marinol®) include treatment of anorexia caused by Acquired Immune Deficiency Syndrome (AIDS) and treatment of chemotherapy-induced nausea and vomiting that is not remedied by standard antiemetics. Dronabinol capsules are available in concentrations of 2.5, 5 and 10 mg. Based upon full prescribing information for patients in the United States (U.S.) that was approved by the U.S. Food and Drug Administration (FDA) [available on the manufacturer’s website (http://www.rxabbvie.com/)], the starting dosage for AIDS wasting is 2.5 mg twice daily one hour
before lunch and dinner whereas the starting dosage for chemotherapy-induced nausea is 5 mg/m²
in intervals before and after chemotherapy for a total of 4 to 6 daily doses. Abuse- or dependence-
related research use of dronabinol in humans generally employs bolus oral doses that are
substantially higher, as described in sections 7B and 8B of this pre-review.

1.1.1 Stereochemical Variants

With exception of dronabinol (as described above), the stereochemical variants of Δ⁹-THC are not
routinely administered.

1.2 Pharmacokinetics

In humans, the predominant route of administration of Δ⁹-THC that is not contained in or extracted
from the cannabis plant is oral (i.e., dronabinol). For this reason, discussion of its pharmacokinetics
will concentrate on the oral route of administration. Two excellent comprehensive reviews served
as the basis for much of this section.¹,²

Compared to absorption of Δ⁹-THC in smoked cannabis, absorption of Δ⁹-THC following oral
ingestion is slow and maximal plasma levels are lower, typically resulting in flatter concentration-
time curves.² Peak plasma levels typically occur in 60-120 minutes after ingestion; however, delays
of up to 4-6 hours have also been reported.³ Rate of absorption may be affected by dose, vehicle,
degradation of the drug in the gut, individual differences in physiology, and the presence/absence
of food.²,³ Estimated bioavailability averages 6%, with considerable variability among individuals.⁴
Ingestion is accompanied by significant first-pass metabolism in the liver, further decreasing the
amount of Δ⁹-THC that reaches sites of action.

Due to its high lipophilicity, Δ⁹-THC is highly bound to plasma proteins and is readily distributed to
highly vascularized tissues (e.g., liver, heart, lung) after absorption.¹ Consequent to significant first-
pass metabolism, plasma-protein binding, and rapid distribution to tissues, plasma levels of Δ⁹-THC
following oral administration fall rapidly, even as pharmacological effects (including centrally
mediated subjective effects) continue.¹,²,⁵ The prolonged cannabinoid behavioral effects, which
occur despite reduced Δ⁹-THC plasma levels, may result from slow elimination of Δ⁹-THC from the
brain, coupled with the cannabimimetic effects of its highly penetrant and equipotent active
metabolite, 11-hydroxy-Δ⁹-tetrahydrocannabinol (11-OH-Δ⁹-THC).³,⁵ Body fat also serves as a
storage reservoir for Δ⁹-THC and its metabolites, as Δ⁹-THC is eliminated from fat tissues even
more slowly than from brain.¹
Metabolism of orally administered Δ⁹-THC occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified.¹ Hydroxylation of the C-11 site to form 11-OH-Δ⁹-THC is the initial step of the biotransformation in most species, including humans.⁶ ⁷ This major metabolite is psychoactive, as indicated by its cannabimimetic effects in mice,⁸ its substitution for Δ⁹-THC in rat drug discrimination,⁹ and its similar psychological effects in men.⁵ ¹⁰ Data from early studies suggested that 11-OH-Δ⁹-THC may have greater brain penetrance than Δ⁹-THC.¹ Further, whereas cannabis smoking results in low brain levels of 11-OH-Δ⁹-THC (vs Δ⁹-THC), approximately equal concentrations of the parent compound and its psychoactive metabolite have been observed following oral administration.² Although hydroxylation of Δ⁹-THC at C-11 to form 11-OH-Δ⁹-THC is most common, hydroxylation may also occur at C-8, resulting in formation of 8α-OH-THC and 8β-OH-THC in rodents⁶ and 8α-OH-THC in human hepatic microsomes.¹¹ I.v. administration of the epimers to a small sample of men revealed that both epimers were active, but potency of the 8α-epimer exceeded that of the 8β-epimer.¹² The primary CYP isoenzymes that catalyze the hydroxylation reactions are CYP2C9 and CYP3A4.¹¹ ¹³ A secondary metabolite, 11-nor-9-carboxy-Δ⁹-tetrahydrocannabinol (11-COOH-Δ⁹-THC or THC-COOH), is formed through oxidation of 11-OH-Δ⁹-THC.¹⁴ THC-COOH lacks cannabimimetic effects and is further metabolized to its glucuronide conjugate, which is water soluble and excreted in urine.² ¹³ Due to its extensive metabolism, relatively little Δ⁹-THC is eliminated from the body unchanged. Δ⁹-THC is excreted primarily in the feces (65-80%) and in the urine (20-35%).¹

1.2.1 Stereochemical Variants

In most of the studies described in this section, the material evaluated was referred to as “Δ⁹-THC,” without reference to stereochemical variants. However, (-)-trans-Δ⁹-THC (dronabinol) is the naturally occurring isomer and, likely was the tested substance. The metabolism of (+)-trans-Δ⁹-THC was reported in a single study.¹⁵ Similar to the (-)-trans-isomer, hydroxylation was a primary mechanism in the biotransformation of (+)-trans-Δ⁹-THC. In this initial step, (+)-trans-Δ⁹-THC was converted to 11-OH-(+)-trans-Δ⁹-THC. Hydroxylation at C-8 was less prominent for (+)-trans-Δ⁹-THC. Further, unlike with 11-OH-( -)-trans-Δ⁹-THC, oxidation of 11-OH-(+)-trans-Δ⁹-THC to its carboxylic acid (i.e., THC-COOH) was minimal. Research on the pharmacokinetics of (-)- and (+)-cis-Δ⁹-THC was not found.
1.3 Pharmacodynamics

When administered to animals, Δ⁹-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).¹⁶⁻¹⁸ These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.¹⁹ Within this endocannabinoid system, two cannabinoid receptors, CB₁ and CB₂, have been identified.²⁰, ²¹ While CB₁ receptors are widespread and abundant in the brain and periphery, CB₂ receptors are confined primarily to the periphery,²² although recent evidence suggests that CB₂ receptors may be present in the brain under certain conditions.²³ Δ⁹-THC is a partial agonist at both types of cannabinoid receptors, at approximately equal affinities (Ki = 41 and 36 nM for CB₁ and CB₂ receptors, respectively).²⁴ Its 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 Δ⁹-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.²⁵ Similarly, the reinforcing effects of THC in squirrel monkeys were reversed by rimonabant,²⁶ as were its antinociceptive, hypothermic and cataleptic effects in rodents²⁷ and its induction of static ataxia in dogs.¹⁸ Antagonists of other major neurotransmitter systems (e.g., dopamine, acetylcholine, norepinephrine, mu opioid) did not alter the discriminative stimulus effects of Δ⁹-THC in rats.⁹ Consistent with these in vivo results, Δ⁹-THC does not have significant affinity for non-cannabinoid receptors of these major systems.²⁸ In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64% Δ⁹-THC,²⁹ suggesting that the antagonism results from preclinical Δ⁹-THC antagonism experiments are translational.

While Δ⁹-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.³⁰⁻³³ Hence, activation of this system through exogenous administration of Δ⁹-THC may have widespread indirect effects on modulatory endocannabinoid-induced regulation of these other neurotransmitters.³⁴ Of note, similar to the action of many other drugs of abuse, acute administration of Δ⁹-THC induces dopamine efflux in reward-related brain areas.³¹ In contrast,
withdrawal from Δ⁹-THC after chronic administration is associated with decreased activation of dopamine neurons.³⁵,³⁶

1.3.1 **Stereocchemical Variants**

Research on the pharmacodynamics of the stereochemical variants of Δ⁹-THC has not been reported (with exception of dronabinol, as described above).
2. Dependence Potential

2.1 Animal Studies

Maldonado \(^{37}\) has provided an excellent summary of research on the dependence potential of \(\Delta^9\)-THC in animals. As noted in his review, rapid and profound tolerance develops to numerous acute preclinical effects of \(\Delta^9\)-THC following chronic administration. Pharmacokinetics plays only a minor role in the development of cannabinoid tolerance. Rather, tolerance to \(\Delta^9\)-THC’s centrally mediated effects appears to be primarily pharmacodynamic in nature and is accompanied by substantial downregulation and desensitization of brain CB\(_1\) receptors.

In contrast, \(\Delta^9\)-THC-induced physical dependence is less robust. Several studies noted the lack of somatic signs of withdrawal following abrupt termination of chronic dosing with \(\Delta^9\)-THC in male rodents, as reviewed in \(^{37, 38}\). Similarly, female rodents also exhibit few somatic signs of withdrawal after termination of chronic \(\Delta^9\)-THC treatment. \(^{39}\) In rhesus monkeys, however, cessation of \(\Delta^9\)-THC treatment resulted in decreases in responding for food reinforcement. \(^{40}\) These results suggest that spontaneous withdrawal from \(\Delta^9\)-THC produces more subtle changes in behavior that contrast with the prominent physical signs observed with some other abused substances (e.g., opioids, alcohol).

Whereas only weak physical signs of withdrawal are observed with spontaneous termination of repeated \(\Delta^9\)-THC administration, antagonist-precipitated withdrawal is associated with more pronounced signs. In rodents, rimonabant administration induces somatic signs such as wet dog shakes, paw tremors, facial rubbing and ataxia as well as behavioral signs such as suppression of operant responding for food. \(^{39, 41-46}\) Rimonabant-precipitated withdrawal has also been reported in rhesus monkeys and in dogs. \(^{18, 47}\)

2.1.1 Stereochemical Variants

Research on the dependence potential of the stereochemical variants of \(\Delta^9\)-THC in animals has not been reported.

2.2 Human Studies

Limited research has examined the dependence potential of \(\Delta^9\)-THC specifically (versus cannabis). Early work found that oral administration of \(\Delta^9\)-THC (10-30 mg) every four hours up to a total daily dose of 210 mg produced reliable acute ratings of “high” and increases in heart rate that dissipated as time elapsed and with repeated administration, suggesting the development of rapid
tolerance. A probe test with a marijuana cigarette during the repeated dosing regimen indicated cross-tolerance also occurred in the participants. During placebo substitution intervals, symptoms of withdrawal were observed, including hyperactivity, increased salivation, irritability, and marked changes in sleep architecture. With exception of sleep disruption (which lasted for up to seven nights), most withdrawal symptoms were alleviated within 96 hours or immediately if participants re-administered Δ⁹-THC.

A later study with lower Δ⁹-THC doses (80-120 mg daily, p.o.) demonstrated similar development of tolerance to the subjective effects of Δ⁹-THC, but not to its appetite enhancing effects. Abrupt cessation of administration after a 4-day repeated dosing regimen resulted in symptoms of withdrawal, including irritability, restlessness, and sleep disruption. In contrast, when the duration of repeated oral Δ⁹-THC administration was shortened to 3 days, development of tolerance and physical dependence no longer occurred. Notably, in all of these laboratory-based studies, oral Δ⁹-THC doses greatly exceeded recommended dronabinol dosage for the treatment of AIDS-associated wasting and chemotherapy-induced nausea.

2.2.1 Stereochemical Variants

Research on the dependence potential of the stereochemical variants of Δ⁹-THC in humans has not been reported.
3. Abuse Potential

3.1 Animal Studies

In animals, the abuse potential of \( \Delta^9 \)-THC has been evaluated in i.v. self-administration and drug discrimination procedures. Because early attempts to train animals to self-administer \( \Delta^9 \)-THC did not result in reliable i.v. self-administration,\(^{51, 52}\) reviews written during the 1980s and 1990s commonly noted that cannabinoids were “false negatives” in the self-administration model.\(^{53}\) Then, in 2000, successful acquisition of \( \Delta^9 \)-THC self-administration was described in squirrel monkeys previously trained to self-administer i.v. cocaine.\(^{54}\) Investigators from the same lab systematically replicated this finding in drug-naïve squirrel monkeys.\(^{55}\) These studies showed that \( \Delta^9 \)-THC produced a typical U-shaped dose-effect function over a dose range of 1-8 \( \mu \)g/kg/infusion (i.v.), with peak responding at 4 \( \mu \)g/kg/infusion.\(^{56}\) In several follow-up studies from this lab, the endocannabinoids, anandamide and 2-arachidonoylglycerol, were shown to be reinforcing in \( \Delta^9 \)-THC-trained monkeys and the reinforcing effects of \( \Delta^9 \)-THC were reversed by rimonabant.\(^{26, 57, 58}\) In rats, investigators have continued to note difficulties in training a robust i.v. \( \Delta^9 \)-THC self-administration,\(^{59, 60}\) although self-administration of the synthetic aminoalkylindole cannabinoid, WIN55,212-2, has been reported in at least two labs.\(^{60-62}\)

In contrast with its variable reinforcing effects in the self-administration model, \( \Delta^9 \)-THC produces robust discriminative stimulus effects in several species, including rats (i.p.),\(^{9}\) rhesus monkeys (i.m.),\(^{63, 64}\) mice (i.p.),\(^{65, 66}\) and pigeons (i.m.).\(^{67}\) In rodents and/or rhesus monkeys, full substitution for \( \Delta^9 \)-THC has been demonstrated for cannabinoids that have been reported to be “marijuana-like” in humans, including \( \Delta^{8} \)-THC (i.p. in rats; i.m. in rhesus monkeys and pigeons), cannabiol (i.p. in rats; i.m. in pigeons), hashish (smoke exposure in rats), CP55,940 (i.m. in rhesus monkeys; i.p. in rats), WIN55,212-2 (i.m. in rhesus monkeys; i.p. in rats), and an array of abused synthetic cannabinoids (e.g., JWH-018, XLR-11, UR-144, AB-CHMINACA; i.p. in rodents; i.m. in rhesus monkeys).\(^{9, 63, 64, 68-73}\) Conversely, cannabidiol (route), a cannabis plant-derived constituent that does not have psychoactive effects in humans, fails to substitute in pigeons (i.m.) or rats (i.p.) trained to discriminate \( \Delta^9 \)-THC from vehicle.\(^{9, 69, 74}\) Further, pharmacological specificity is indicated by the lack of generalization from THC observed after administration of drugs from a wide variety of non-cannabinoid classes, including antipsychotics, opioid (mu, delta, and kappa) agonists, tricyclic antidepressants, dissociative anesthetics, barbiturates, stimulants, muscarinic agonists, nicotine, and GABA agonists.\(^{9, 64, 68, 75, 76}\) Although partial substitution has been reported with
diazepam, this effect is accompanied by significant decreases in overall responding and cross-substitution in rats trained to discriminate diazepam from vehicle does not occur.Δ9-THC’s discriminative stimulus effects are attenuated by prior administration of a selective CB1 receptor antagonist (e.g., rimonabant), but not by the selective CB2 receptor antagonist SR144528. These effects are also not reversed by antagonists of other major neurotransmitter systems, including dopamine, acetylcholine, norepinephrine, and mu opioid.

Cross-substitution of Δ9-THC in animals trained to discriminate other cannabinoids also has been reported. Δ9-THC generalizes from Δ8-THC, CP55,940, and JWH-018 in rodents. Δ9-THC has been evaluated in several discrimination procedures in which non-cannabinoid drugs served as the training stimulus. The results of these studies show that it did not substitute for diazepam, mephedrone, cocaine, d-amphetamine, or phencyclidine, providing additional evidence of the pharmacological selectivity of Δ9-THC’s discriminative stimulus effects.

3.1.1 Stereochemical Variants

The most commonly cited source of Δ9-THC used in the research described above was the NIDA Drug Supply Program which provides synthetic (-)-trans-Δ9-THC to researchers. Limited work has examined specific effects of the other three stereochemical variants of Δ9-THC. Although early studies reported that the (+)-Δ9-THC stereoisomers were considerably less potent in vivo than the (-)-Δ9-THC stereoisomers, these studies were not conducted using optically pure enantiomers. However, as improvements in synthetic methods led to enhanced purity, these initial findings have been upheld. For example, Martin et al. reported that (-)-trans-Δ9-THC was at least ten-fold more potent in the dog static ataxia model than (+)-cis-Δ9-THC or (+)-trans-Δ9-THC, neither of which produced the full syndrome at the highest dose that the limited drug quantities allowed. In addition, (-)-trans-Δ9-THC exhibited 10-fold greater hypothermic effect in mice and was 100-fold more potent at decreasing schedule-controlled responding in rhesus monkeys than (+)-Δ9-THC. Similarly, greater potencies were noted for (-)-trans-Δ8-THC and -11-OH-Δ8-THC-dimethylheptyl than for their (+)-isomers, suggesting that the psychoactivity of the tetrahydrocannabinols is stereoselective and resides in their naturally occurring (-)-stereoisomers.

3.2 Human Studies

With few exceptions, human studies relevant to the abuse potential of pure or synthetic Δ9-THC (i.e., excluding cannabis and plant-derived extracts) have used dronabinol and an oral route of
administration. In controlled laboratory settings, self-administration of dronabinol has been demonstrated; however, results suggest that it is a weak reinforcer at best. First, self-administration was variable, in that subjects chose to take dronabinol only during about 50% of the opportunities it was offered. Second, if given the opportunity to choose a marijuana cigarette instead of oral $\Delta^9$-THC, 80% of the study participants preferred the marijuana cigarette. In addition, dronabinol does not appear to be abused outside of the laboratory. A multi-method review that incorporated findings from the scientific and product safety literature as well as interviews with physicians and perusal of the popular press revealed little evidence that oral dronabinol was used for non-medical purposes. Phenomena such as “doctor-shopping” or “script-chasing” were not common and dose escalation did not typically occur with continued medicinal administration.

Although oral $\Delta^9$-THC is a weak reinforcer, it has robust subjective effects that resemble those of cannabis. Male and female study participants readily distinguish oral $\Delta^9$-THC (7.5 mg) as being “marijuana-like” and as different from alcohol (0.8 g/kg) or d-amphetamine (20 mg). On a Capsules Rating Form that is sensitive to cannabinoid drugs, $\Delta^9$-THC (dronabinol, 10 and 20 mg) was associated with increased ratings of “strong drug effect,” with peak effect occurring at 90 minutes post-administration. Further, when oral or smoked $\Delta^9$-THC was compared directly to cannabis administered via the same route of administration, both $\Delta^9$-THC and cannabis (each containing 8.4 or 16.9 mg $\Delta^9$-THC) produced a similar profile of subjective effects on the Addiction Research Center Inventory, including increased feelings of “drug effect,” experience of a “drug high,” and increased ratings on the Marijuana scale. Oral administration of $\Delta^9$-THC or cannabis produced greater sedation whereas smoking either substance failed to do so. Both substances produced dose-dependent increases in plasma $\Delta^9$-THC levels, beginning immediately after smoking and at approximately 60 minutes after oral administration. Naltrexone (a mu-opioid receptor antagonist) did not reverse these subjective effects of oral dronabinol.

In addition to evaluation of self-reported subjective effects, dronabinol has been examined in a series of studies using a more traditional drug vs. placebo discrimination procedure, in which participants successfully acquired a discrimination based upon a training dose of 25-30 $\Delta^9$-THC. $\Delta^9$-THC produced dose-dependent substitution for the training dose in participants of both sexes and self-reported subjective effects resembled those noted in previous studies that relied entirely on survey measures. As in the animal studies, $\Delta^9$-THC discrimination was
pharmacologically selective (to the extent tested), with triazolam (a positive modulator of the GABA-A receptor), hydromorphone (a mu-opioid agonist), and methylphenidate (a dopamine reuptake inhibitor) failing to substitute for $\Delta^9$-THC in the discrimination procedure.\textsuperscript{100}

3.2.1 **Stereochemical Variants**

Research on the abuse potential of the stereochemical variants of $\Delta^9$-THC in humans has not been reported.
4. References


Järbe TU, Henriksson BG. Discriminative response control produced with hashish, tetrahydrocannabinols (delta 8-THC and delta 9-THC), and other drugs. Psychopharmacologia. 1974;40(1):1-16.