WHO Expert Committee on Drug Dependence Pre-Review

Extracts and tinctures of cannabis

Section 2: Pharmacology

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1. **General Pharmacology**

Studies to be included in the report are those involving:

- Cannabis extracts
  - Cannabis tinctures
  - Cannabis oils
  - Aqueous extracts
- Nabiximols

All products mentioned above are extracts derived from the cannabis plant, usually from dried and cured inflorescence (flowering heads plus resin-containing trichomes). Trichomes are especially rich in cannabinoids and terpenes (i.e., aromatic oils that are released upon heating and give cannabis inflorescences and extracts their characteristic odors and tastes). The purpose of the extraction process is to separate and concentrate the desired constituents of the plant (i.e., cannabinoids, terpenes) and to discard undesirable constituents (e.g., chlorophyll, tar and other extraneous plant matter). The process through which extraction is accomplished determines the classification of the resultant product (i.e., tincture, oil, aqueous extract). The potency of the final product is determined by the concentration of active cannabinoids (namely \( \Delta^9 \)-tetrahydrocannabinol; \( \Delta^9 \)-THC) contained in the inflorescence as well as by the efficiency of the extraction process. Nabiximols is a standardized proprietary blend of \( \Delta^9 \)-THC and cannabidiol (CBD) extracted from the cannabis plant and formulated into an oromucosal spray.

1.1 **Routes of administration and dosage**

“Dosage” of cannabis extracts most often refers to amount of \( \Delta^9 \)-THC contained in the preparation (and its ratio to CBD, if the extract contains both compounds). In humans, cannabis extracts may be delivered through various routes of administration, including sublingual, oral, inhalation (smoking or vaping), rectal, and transdermal. With exception of nabiximols, which has recommended doses, dosage of cannabis extracts is self-determined by the user and may change over time due to the development of tolerance. Route of administration affects the ease with which dosage may be self-titrated. When a cannabis extract is vaped, its psychoactive effects occur rapidly, allowing users a quick way to assess their intake relative to past uses. Although this rapid feedback would allow titration of dose to desired effect with extracts containing different concentrations of \( \Delta^9 \)-THC, research has shown that titration is usually partial: users who smoke or vape products with higher \( \Delta^9 \)-THC contents than their regular product tend to up-titrated, resulting in greater overall
exposure. In addition, cannabis extraction techniques may result in variable Δ⁹-THC yield in the final product and precise measurement of Δ⁹-THC and CBD levels in available products often is lacking. Self-determination of dosage of orally administered cannabis extracts has the extra complication of a delayed onset of action. Below, typical routes of administration for each of the extracts covered in this report are discussed separately.

1.1.1 Cannabis tinctures

Cannabis tinctures are cannabis extracts for which extraction is accomplished through use of ethanol as a solvent for the cannabinoids contained in crushed cannabis inflorescence or other parts of the plant. Efficiency of the process is enhanced through use of higher concentrations of ethanol; for example, 80-90% ethanol yields tinctures with ten times higher Δ⁹-THC concentrations than those made with 40% ethanol. These alcohol-based preparations usually are delivered sublingually or used to infuse edibles or beverages (i.e., oral administration).

1.1.2 Cannabis oils

Cannabis oils are typically derived through using a hydrocarbon solvent (e.g., butane, propane) to extract Δ⁹-THC (or other desired cannabinoids) from cannabis, although other solvents or processes (e.g., carbon dioxide, ice water extraction) are also possible. The resulting product may differ in consistency from runny oil to butter, wax, and shatter (in increasing order of viscosity). Because Δ⁹-THC is highly soluble in lipids, oil extracts tend to be stable over longer periods of time and often contain high Δ⁹-THC concentrations. Oils may be incorporated into food or beverage for oral administration or may be vaped or “dabbed.”

1.1.3 Aqueous cannabis extracts

Aqueous cannabis extracts are extracts that are derived through use of water to extract cannabinoids from the cannabis plant. These extracts are most often used as a tea-like beverage. Δ⁹-THC’s poor solubility in water limits its concentration in aqueous solutions; hence, aqueous cannabis extracts are notably weak and stability of the formulation over time is poor.
1.1.4 Nabiximols (Sativex®)

Nabiximols (Sativex®) is a cannabis extract formulated into an oromucosal spray. It has been approved for medical use in some European countries and in Canada, while still under review by the Food and Drug Administration in the United States. Each “puff” of nabiximols contains 2.7 mg Δ⁹-THC and 2.5 mg CBD as well as small concentrations of minor cannabinoids and terpenes contained in the specially bred cannabis from which nabiximols is extracted. The typical dose is two puffs, administered up to 4 times daily. Absorption occurs through the buccal membrane or sublingually, dependent upon where the spray is directed in the oral cavity. It is marketed as an adjunctive treatment for spasticity and neuropathic pain associated with multiple sclerosis and has also been employed as a treatment for pain caused by advanced cancer.

1.2 Pharmacokinetics

Δ⁹-THC and/or CBD are the primary targets for cannabis extractions, with terpenes sometimes included as a secondary target. The ratio of Δ⁹-THC:CBD contained in an extract is determined by the ratio of these cannabinoids in the plant strain and by the choice of part(s) of the plant used to make the extract. For example, hemp seed oil contains negligible concentrations of Δ⁹-THC and CBD because the hemp seeds from which it is derived have low concentrations of these cannabinoids. In contrast, cannabis plants bred for recreational use typically have high Δ⁹-THC concentrations with negligible CBD content whereas those bred for medicinal use may have comparable levels of both compounds (e.g., nabiximols) or high concentrations of CBD and negligible Δ⁹-THC (e.g., pure CBD oil; excluded from this report).

In the plant, Δ⁹-THC is present primarily in its acid form, Δ⁹-THCA, which is rapidly decarboxylated to Δ⁹-THC upon heating or burning, as occurs during smoking or in many, but not all, extraction processes. Consequently, the bulk of the extant research on cannabis pharmacokinetics has focused on Δ⁹-THC. This section will begin with a discussion of the pharmacokinetics of Δ⁹-THC delivered via routes of administration common for extracts (i.e., inhalation via vaping; oral via consumption in edibles or beverages; sublingual via tinctures) and will end with a discussion of the pharmacokinetics of nabiximols.
Two excellent comprehensive reviews served as the basis for much of this section on Δ⁹-THC. Route of administration strongly affects the absorption of Δ⁹-THC contained in the extracts and its time course. As mentioned above (section 4A), extracts are administered through several routes of administration: inhalation (vaping), oral (food or beverage), or sublingual (tinctures).

Combustion byproducts (e.g., tar, ammonia, carcinogens) are a concern with smoking cannabis, as they are with smoked tobacco. Consequently, inhalation of cannabis extracts (primarily oils) using stationary or portable vaporizers (including vape pens) has increased. Research on possible impact on the pharmacokinetics, pharmacodynamics and toxicological effects of vaping cannabis extracts (as compared with smoking cannabis) has not yet caught up with this recent trend. In the few studies that have been done, pharmacokinetic profiles of vaped versus smoked cannabis / cannabis extracts appear to be similar. For example, Hazekamp et al. found that inhalational administration of pure Δ⁹-THC or Δ⁹-THC contained in bulk cannabis using a Volcano® vaporizer resulted in comparable exhaled concentrations of Δ⁹-THC. Based upon studies of smoked cannabis, absorption of Δ⁹-THC from inhalation is rapid and measurable levels are observed in plasma seconds after the first puff. While peak plasma levels typically occur in 3-10 minutes after smoking, peak “highs” do not occur until 20-30 minutes after smoking, although others have reported an earlier peak. Because Δ⁹-THC concentrations in the plasma may have already started to fall before maximal effect, plasma levels are not the best predictor of intoxication. Bioavailability of Δ⁹-THC after cannabis smoking or vaping 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. In addition, approximately 30-40% of the Δ⁹-THC concentration inhaled through smoking or vaping is directly exhaled, suggesting incomplete pulmonary absorption.

Compared to absorption of Δ⁹-THC in inhaled cannabis, absorption of Δ⁹-THC following oral ingestion is slow and maximal plasma levels are lower, typically resulting in flatter concentration-time curves. Peak plasma levels typically occur in 60-120 minutes after ingestion; however, delays of up to 4-6 hours have also been reported. 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. Estimated bioavailability averages 6%, with considerable variability among individuals. Ingestion is accompanied by significant first-pass metabolism in the liver, further decreasing the amount of Δ⁹-THC that reaches sites of action.
Absorption of Δ⁹-THC after sublingual administration has not been investigated extensively, except in the context of extracts containing mixtures of cannabinoids (e.g., nabiximols, as discussed below). Two of the sparse studies that specifically examined absorption of Δ⁹-THC after sublingual administration found that its bioavailability was improved when administered to rabbits in a vehicle containing beta-cyclodextrin (as compared to oral administration). The authors suggested that cyclodextrin-induced increase in Δ⁹-THC aqueous solubility may have contributed to this enhanced bioavailability. In humans, only minor differences in oral and sublingual absorption of a Δ⁹-THC formulation (> 98% pure; Namisol®) were observed, with plasma Δ⁹-THC levels showing slightly lower peaks and slower elimination following sublingual administration. Whether the amount of alcohol delivered with Δ⁹-THC in sublingual tincture preparations would affect its pharmacokinetics has not been determined.

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. First-pass metabolism (with oral administration only), plasma-protein binding and rapid distribution to tissues contribute to rapidly falling plasma levels of Δ⁹-THC following absorption, even as pharmacological effects (including centrally mediated subjective effects) continue. These 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). 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.

Metabolism of Δ⁹-THC contained in cannabis extracts occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified. Hydroxylation of the C-11 site to form 11-OH-Δ⁹-THC is the initial step of the biotransformation in most species, including humans. This major metabolite is psychoactive, as indicated by its cannabimimetic effects in mice, its substitution for Δ⁹-THC in rat drug discrimination, and its similar psychological effects in men. Data from early studies suggested that 11-OH-Δ⁹-THC may have greater brain penetrance than Δ⁹-THC. However, unlike with orally administered Δ⁹-THC, cannabis smoking (and presumably vaping) results in low brain levels of 11-OH-Δ⁹-THC (vs Δ⁹-THC). 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 8β-OH-THC and 8α-OH-THC in rodents and 8β-OH-THC in human hepatic microsomes. I.v. administration of the epimers to a small sample of men revealed that both
epimers were active, but potency of the 8β-epimer exceeded that of the 8α-epimer.\textsuperscript{35} The primary CYP isoenzymes that catalyze the hydroxylation reactions are CYP2C9 and CYP3A4.\textsuperscript{34, 36} 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.\textsuperscript{37} THC-COOH lacks cannabimimetic effects and is further metabolized to its glucuronide conjugate, which is water soluble and excreted in urine.\textsuperscript{14, 36} 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%).\textsuperscript{13}

1.2.1 Nabiximols

Δ9-THC and CBD are the two primary constituents in nabiximols. The pharmacokinetics of Δ9-THC are described above. The pharmacokinetics of CBD resemble those of Δ9-THC.\textsuperscript{13} Absorption of smoked CBD is rapid, with bioavailability averaging about 6% after oral administration.\textsuperscript{38} As seen with Δ9-THC, primary metabolism occurs via oxidation,\textsuperscript{14} with 7-hydroxy-CBD and CBD-7-oic acid as major metabolites.\textsuperscript{39, 40} However, unlike with Δ9-THC, a high percentage of CBD is eliminated unchanged in the feces.\textsuperscript{13, 14}

Pharmacokinetic investigation with nabiximols reveals considerable individual variability, as is characteristic of cannabinoids.\textsuperscript{9, 14} Absorption of Δ9-THC and CBD are rapid following sublingual administration of nabiximols, with slightly higher bioavailability for Δ9-THC than CBD.\textsuperscript{9} Enhanced levels of plasma 11-OH-Δ9-THC suggest that a portion of the drug may be delivered orally (i.e., swallowed) rather than sublingually.\textsuperscript{41} Multiple doses do not result in significant accumulation in plasma.\textsuperscript{9}

Animal work has suggested that CBD may hinder or delay Δ9-THC metabolism through competition for or inactivation of CYP P450 enzymes,\textsuperscript{42, 43} resulting in enhancement of Δ9-THC’s in vivo effects.\textsuperscript{44} However, this research generally used higher concentrations of CBD (in relation to Δ9-THC concentration) than are typically present in most cannabis strains or in nabiximols. In contrast, lower CBD concentrations failed to accentuate Δ9-THC’s effects in rodents.\textsuperscript{44} 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 Δ9-THC:CBD normally seen in cannabis or in nabiximols.\textsuperscript{13, 41, 45, 46} Further, the results of a study on the pharmacokinetics of nabiximols in a small sample of cannabis users is supportive of this hypothesis.\textsuperscript{41}
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. However, except for Δ⁹-THC and CBD (in some plants), most of these other compounds are present in the plant in relatively small quantities. In addition, the extraction process is designed to concentrate the desired constituents (usually Δ⁹-THC and/or CBD). Hence, the degree to which other compounds may contribute to the array of pharmacological and behavioral effects produced by cannabis extracts is largely unknown. The discussion below focuses primarily on the pharmacodynamics of Δ⁹-THC followed by a summary of the pharmacodynamics of hemp seed oil and nabiximols. The predominance of Δ⁹-THC-like effects are dependent upon how much of Δ⁹-THC is contained in the extract, how much of the extract is consumed, and its route of administration.

1.3.1 Cannabis Extracts: Focus on Δ⁹-THC

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). These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions. Within this endocannabinoid system, two cannabinoid receptors, CB₁ and CB₂, have been identified. While CB₁ receptors are widespread and abundant in the brain and periphery, CB₂ receptors are confined primarily to the periphery, although recent evidence suggests that CB₂ receptors may be present in the brain under certain conditions. 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). Further, the affinities of cannabis vapor (created in Volcano® vaporizer) and pure Δ⁹-THC for the CB₁ receptor are similar for cannabis extract containing an equivalent amount of Δ⁹-THC, emphasizing the degree to which Δ⁹-THC is predominant in the pharmacology vaped cannabis extract. Δ⁹-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 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. Similarly, the
reinforcing effects of THC in squirrel monkeys were reversed by rimonabant, as were its antinociceptive, hypothermic and cataleptic effects in rodents and its induction of static ataxia in dogs. 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. Consistent with these in vivo results, Δ⁹-THC does not have significant affinity for non-cannabinoid receptors of these major systems. In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64-2.78% Δ⁹-THC, 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. 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. 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. In contrast, withdrawal from Δ⁹-THC after chronic administration is associated with decreased activation of dopamine neurons.

### 1.3.2 Hemp Seed Oil

Hemp seed oil may be extracted via a cold-pressing process from the seeds of cannabis plants that contain negligible amounts of Δ⁹-THC (typically < 0.3% in the U.S. and < 0.2% in the EU). Alternatively, it is extracted from cannabis plants that contain Δ⁹-THC and CBD, but only the seeds (which do not contain Δ⁹-THC) are used. In the latter case, Δ⁹-THC, CBD, or their acidic analogs (THCA and CBDA, respectively) may be present as contaminants resulting from harvesting, extraction, or storage processes. Unlike cannabis extracts that contain high Δ⁹-THC concentrations, hemp seed oil is used primarily for its putative nutritional benefits, as the oil is rich in unsaturated fatty acids (e.g., 3-, 6- and 9-omega) and proteins. In small-sample studies, hemp seed oil did not produce Δ⁹-THC-like psychoactive effects when consumed orally or inhaled.

### 1.3.3 Nabiximols: Δ⁹-THC and CBD extract

Nabiximols is a botanical extract of the cannabis plant. Ninety percent of the medication is comprised of a combined ~ 1:1 ratio of Δ⁹-THC and CBD, with other minor cannabinoids and
terpenes comprising the remaining plant-derived ingredients. Given their high concentrations, Δ⁹-THC and CBD undoubtedly play a role as primary contributors to nabiximols’ pharmacological effects. As discussed above, many of the major psychoactive and therapeutic effects of Δ⁹-THC are mediated through its interaction with CB₁ and/or CB₂ receptors. However, unlike Δ⁹-THC, CBD has minimal affinity for CB₁ receptors and it does not produce cannabimimetic pharmacological or subjective effects in animals or humans.⁷⁸, ⁷⁹ Animal research has posited various potential therapeutic indications for CBD, including as a treatment for epilepsy, pain and inflammation, anxiety, and psychosis.³⁸, ⁸⁰, ⁸¹ While the effectiveness of CBD for many of these indications has not been explored, extant evidence suggests that it may have efficacy for the treatment of severe refractory epilepsy (e.g., Dravet syndrome).⁸², ⁸³ Hence, CBD may have pharmacological effects independent of any interaction with Δ⁹-THC. Putative mechanisms through which CBD may produce its pharmacological effects include activation of transient receptor potential vanilloid 1 (TRP-V1) channels or 5-HT₁₆ receptors, antagonism of alpha₁ adrenergic or mu opioid receptors, or antagonism of GPR55, an orphan G-protein coupled receptors.³⁸, ⁸⁴, ⁸⁵

While the degree to which CBD’s independent effects contribute to nabiximols’ therapeutic profile is unclear, previous research with Δ⁹-THC and CBD combinations has suggested that CBD is not likely to contribute to the cannabimimetic subjective effects that have been observed at acute supratherapeutic nabiximols doses.⁸⁶, ⁸⁷ Further, interactions among Δ⁹-THC, CBD, and the other minor cannabinoids and terpenes present in nabiximols have also been posited to contribute to the overall therapeutic benefit of nabiximols through an “entourage” effect.⁸⁸-⁹⁰ The mechanism(s) through which an “entourage” effect might work to effect nabiximols’ therapeutic and adverse effect profile has not been completely delineated. The hypothesis that CBD-induced inhibition of Δ⁹-THC pharmacokinetics may contribute to nabiximols’ effects has not been supported by research in humans.⁴¹, ⁴⁵
2. Dependence Potential

2.1 Animal Studies

Although the dependence potential of cannabis extracts has not been studied explicitly in animals, \( \Delta^9 \)-THC, the primary psychoactive constituent in many extracts, has been investigated in numerous studies, as reviewed by Maldonado.\(^91\) In rodents, only weak physical signs of withdrawal are observed with spontaneous termination of repeated \( \Delta^9 \)-THC administration. In contrast, antagonist-precipitated withdrawal is associated with more pronounced signs. 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.\(^92,98\) Rimonabant-precipitated withdrawal from \( \Delta^9 \)-THC has also been reported in rhesus monkeys and in dogs.\(^53,99\)

2.1.1 Nabiximols

The dependence potential of nabiximols has not been evaluated in animals.

2.2 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.\(^100,101\) 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.\(^102-106\) 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,\(^107\) although disruption of sleep may linger.\(^108\)

The dependence potential of cannabis extracts has not been specifically evaluated; however, previous studies show that regular exposure to cannabis containing high concentrations of \( \Delta^9 \)-THC increases the probability and severity of dependence.\(^105,109,110\) These results suggest that regular use of some types of extracts would be more likely to be associated with dependence than others. For example, due to the limited solubility of \( \Delta^9 \)-THC in water, its concentration is relatively low in
aqueous extracts (e.g., estimated at 10 mg Δ⁹-THC per liter of aqueous solution). In tinctures, Δ⁹-THC concentration is highly affected by the percentage of ethanol in the vehicle, with 80-90% ethanol resulting in tinctures with higher Δ⁹-THC concentrations than those made with 40% ethanol. Given the notable lipid solubility of cannabinoids, including Δ⁹-THC, cannabis oil extracts contain the highest Δ⁹-THC concentrations and would be expected to have the highest potential for dependence. In addition to cannabis oil extracts that are used primarily for making cannabis edibles and for vaping, cannabis oil extracts include products such as wax and shatter in which Δ⁹-THC is highly concentrated. In surveys of college students and regular cannabis users, frequent use of butane hash oil, a high-potency product, was associated with greater dependence and perceived lack of control over cannabis use.

2.2.1 Nabiximols

Although the dependence potential of nabiximols has not been evaluated in humans, an earlier review of its abuse and dependence potential mentioned an unpublished study, in which 44% of patients who experienced a 2-week interruption of nabiximols treatment exhibited an increase in some signs of cannabis withdrawal (e.g., disrupted sleep). Other studies have examined the efficacy of nabiximols for the treatment of cannabis withdrawal syndrome and reported that it was effective in ameliorating withdrawal symptoms in treatment and non-treatment seeking cannabis users.
3. Abuse Potential

3.1 Animal Studies

Cannabis extracts vary in the concentration(s) of Δ⁹-THC and/or CBD they contain and their typical route of administration (e.g., inhalation via vaping, oral, sublingual). Of these two cannabis constituents, only Δ⁹-THC produces classic Δ⁹-THC-like pharmacological effects in animals; available evidence suggests that CBD does not have abuse potential. Hence, most research which has examined the abuse potential of cannabis in animal models has used systemic injection of Δ⁹-THC as a proxy. In a few instances, combusted or aerosolized Δ⁹-THC has been tested. Specific evaluation of cannabis extract (vs. pure Δ⁹-THC) has been rare. Consequently, a major distinguishing factor among these studies is route of administration, a factor that also varies across cannabis extracts. The extant preclinical animal research on the abuse potential of Δ⁹-THC has been discussed in the pre-review of Δ⁹-THC and is summarized here. In addition, results of several recent studies that have explored the use of vaporizers or electronic cigarette technology to expose animals to aerosolized cannabinoids (i.e., animal model of vaping) are described.

Briefly, while robust i.v. self-administration of Δ⁹-THC has been shown in squirrel monkeys, investigators have noted difficulties in training a robust i.v. Δ⁹-THC self-administration in rats, although self-administration of the synthetic aminoalkylindole cannabinoid, WIN55,212-2, has been reported in at least two labs. In contrast, Δ⁹-THC produces robust and pharmacologically selective discriminative stimulus effects in several species, including rats (i.p.), rhesus monkeys (i.m.), mice (i.p.), and pigeons (i.m.). In rodents and/or rhesus monkeys, full substitution for Δ⁹-THC has been demonstrated for other psychoactive phytocannabinoids, CP55,940, WIN55,212-2, and an array of abused synthetic cannabinoids.

Inhalational studies of cannabinoids have used combusted cannabis with defined amounts of Δ⁹-THC and other cannabinoids (e.g., CBD) or they have employed newer methods of vapor exposure using a vaporizer or e-cigarette apparatus to aerosolize Δ⁹-THC, cannabis extract, or synthetic cannabinoids. These studies have shown that exposure to cannabis smoke containing Δ⁹-THC produced a concentration-dependent profile of effects in rodents that is shared with systemically injected Δ⁹-THC: suppression of locomotor activity, antinociception, hypothermia and catalepsy. Similarly, this tetrad of cannabinoid effects was also observed in rats exposed to Δ⁹-THC or crude cannabis extract (containing comparable Δ⁹-THC concentrations), which were aerosolized...
using an e-cigarette apparatus. However, when $\Delta^9$-THC was delivered via a Volcano vaporizer, rats exhibited different effects than when it was administered i.p. Whereas i.p. $\Delta^9$-THC produced conditioned place aversion, aerosolized $\Delta^9$-THC failed to produce this effect or produced conditioned place preference. Locomotor stimulation and increased feeding behavior were also noted with aerosolized $\Delta^9$-THC, but not with i.p. $\Delta^9$-THC. Because determination of exact dose is complicated in inhalational studies using modified vaporizers, the degree to which dose ranges were equivalent for the two routes of administration (i.p. vs. inhalation) was not examined.

3.1.1 Nabiximols

Although the abuse potential of nabiximols has not been explicitly evaluated in animals, its two constituents ($\Delta^9$-THC and CBD) have been tested in tandem in drug discrimination and a place conditioning paradigm. In male Long-Evans rats trained to discriminate 3 mg/kg $\Delta^9$-THC from vehicle, CBD failed to substitute for $\Delta^9$-THC when tested alone at doses up to 10 times the $\Delta^9$-THC training dose. It also did not alter $\Delta^9$-THC’s discriminative stimulus or response rates when tested at CBD:$\Delta^9$-THC ratios of 1:1 to 10:1. In contrast, CBD at 1:1 and 10:1 CBD:$\Delta^9$-THC ratios attenuated the conditioned aversive effects produced by 10 mg/kg $\Delta^9$-THC in ICR mice. In a select group of rats trained to self-administer i.v. $\Delta^9$-THC, CBD also did not affect $\Delta^9$-THC’s reinforcing effects. These results suggest that CBD contained in nabiximols may attenuate the aversive effects of $\Delta^9$-THC, but is unlikely to affect its subjective or reinforcing effects.

3.2 Human Studies

Prior research has suggested that the cannabis constituent responsible for the plant’s reinforcing and subjective effects is $\Delta^9$-THC. Cannabis extracts vary in their average $\Delta^9$-THC concentrations, with butane hash oil containing maximal amounts and aqueous extracts containing the least. Given these differences in $\Delta^9$-THC content, it would not be surprising if the different types of extracts were associated with variations in abuse potential; however, empirical data to support this hypothesis are lacking. The abuse potential of cannabis extracts has not been specifically evaluated in humans. One study with oral administration of cannabis extract containing a 2:1 ratio of $\Delta^9$-THC (20 mg, up to 4 in an acute administration) and CBD found that the most prominent effects were tiredness, dizziness, and drowsiness. These results are consistent with earlier an earlier finding that oral administration of $\Delta^9$-THC or cannabis produced greater sedation than smoking. The abuse potential of high potency cannabis extracts, especially via vaporizer, has not yet been evaluated. However, as use of portable vaporizers (e.g., vape pens and other
devices) increases in popularity among youth and young adults, use of cannabis extracts in these devices is likely to follow, albeit users may continue to employ more than one method to use cannabis (e.g., vaping and smoking).

3.2.1 Nabiximols

A randomized double-blind clinical trial was conducted to evaluate the abuse potential of nabiximols in recreational cannabis users. Participants were administered acute bolus doses of nabiximols containing $\Delta^9$-THC concentrations of 10.8, 21.6, or 43.2 mg and comparable concentrations of CBD. Whereas 10.8 mg did not induce subjective effects associated with cannabis use, cannabis-like effects (e.g., drug-like, stoned, and increased marijuana ratings on the Addiction Research Center Inventory) were reported at higher doses. Notably, however, the usual dose of nabiximols contains a daily total of 21.6 mg $\Delta^9$-THC delivered over the course of 3-4 divided dosings. Karschner et al. reported similar findings with lower doses of nabiximols. Abuse also has not been reported in post-market surveillance of nabiximols.
4. References


117. Manwell LA, Charchoglyan A, Brewer D, Matthews BA, Heipel H, Mallet PE. A vapourized Delta(9)-tetrahydrocannabinol (Delta(9)-THC) delivery system part I: development and validation of a pulmonary


