

WHO Expert Committee on Drug Dependence Pre-Review

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Delta-9-tetrahydrocannabinol

Section 3: Toxicology



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1. Toxicology

The pharmacological activity of Δ^9 -THC is stereoselective: the (-)-trans isomer is 6-100 times more potent than the (+)-trans isomer [1]. The (-)-trans isomer is found naturally in the plant and most scientific and clinical studies have been conducted with the (-)-trans isomer. In synthetic form Δ^9 -THC is known as dronabinol (Marinol) and is available on prescription in several countries as a treatment for chemotherapy-induced nausea and vomiting and HIV-related wasting [2]. Pure Δ^9 -THC is not typically used as a recreational substance, rather being present as the main intoxicating component of smoked cannabis, vaporised cannabis and cannabis extracts and concentrates (see Report 1: Cannabis plant and cannabis resin).

1.1 Lethal dose

The toxicity of Δ^9 -THC is very low compared to most other recreational and pharmaceutical drugs. Following oral administration, the median lethal dose (LD_{50}) was 800 mg/kg in rats [3], up to 3000 mg/kg in dogs and up to 9000 mg/kg in monkeys [4]. It has been calculated that a lethal dose in a 70 kg human would be approximately 4 g [5] and that such a dose could not be realistically achieved in a human following oral consumption, smoking or vaporising the substance, as Δ^9 -THC has a large margin of safety [6]. The absence of mortality with Δ^9 -THC may reflect the low density of cannabinoid CB1 receptors in brainstem regions that control vital cardiovascular or respiratory functions.

1.2 Effects on the cardiovascular system

A recent meta-analysis concluded that acute Δ^9 -THC exposure in humans produces tachycardia with an average increase in heart rate of 8 beats per minute (bpm) [7]. The effects of Δ^9 -THC on cardiovascular function are generally dose-dependent: a dose of 7.5 mg did not affect heart rate or blood pressure, while 12 mg caused tachycardia (mean increase of 4 bpm) without a change in blood pressure [7]. Tolerance may occur to these effects: an early study administered oral Δ^9 -THC to 12 healthy male participants with an escalating dosing regimen over 20 days (up to 210 mg Δ^9 -THC per day; 7 x 30 mg oral doses). While Δ^9 -THC promoted tachycardia early in the treatment period, at later stages it actually *decreased* supine systolic and diastolic blood pressure and decreased heart rate [8]. This highlights that the hemodynamic effects of Δ^9 -THC may vary according to exposure over time. Animal studies have limited relevance to understanding human cardiovascular effects since Δ^9 -THC generally promote bradycardia and hypotension in laboratory animal species, effects that are opposite to those observed in humans.

1.3 Effects on the respiratory system

Δ^9 -THC is a bronchodilator with possible benefit in treating asthma ([9-11], reviewed in [12]). On the other hand, *in vitro* studies indicate that Δ^9 -THC: reduces the viability of human epithelial lung cells; causes oxidative stress; and suppresses apoptosis and mitochondrial function in these cells [13-15]. Δ^9 -THC also induced expression of cytochrome P450 1A1 (CYP1A1) *in vitro*, which activates polycyclic aromatic hydrocarbons and has been linked to lung cancer [16-18]. However, the relevance of these changes to human risk is unknown with no increased lung cancer risk detected in epidemiological studies of cannabis users (see Report 1 on cannabis and cannabis resin). In fact, Δ^9 -THC is considered to have potential therapeutic effects in airway disease by reducing inflammation in airways and increasing lung cancer cell lysis mediated by lymphocyte activated killer cells [19, 20].

1.4 Effects on the immune system

In vitro and *in vivo* animal studies demonstrate that Δ^9 -THC can modulate immune function, and this may reflect pharmacological agonist effects on CB2 cannabinoid receptors. For example, Δ^9 -THC decreases pro-inflammatory Th1 cytokine responses (e.g. decreasing interferon (IFN)- γ and interleukin (IL)-2 production) and increase anti-inflammatory Th2 cytokine responses (e.g. increasing IL-4 and IL-10 production) (reviewed in [21]). However, the Δ^9 -THC doses required in these studies are generally large and may not be relevant to typical human doses [22-24].

Studies administering pure Δ^9 -THC to patients provide more relevant insights into the immunomodulatory effects of the drug. In a large RCT involving multiple sclerosis patients given oral Δ^9 -THC (up to 25 mg/day for 14 weeks) there were no significant effects observed on serum concentrations of IFN γ , IL-10, IL-12 or C-reactive protein [24]. However, this study may have inadequately underpowered to detect such changes. A 3 week RCT involving 22 immunocompromised HIV patients on antiretroviral therapy given Δ^9 -THC (2.5 mg per day) found no effects on: the percentage of CD4+ and CD8+ T cells; resting or activated T cells; natural killer cell number; and on immune responses to *Staphylococcal* enterotoxin B, cytomegalovirus (CMV), phytohemagglutinin, tetanus toxin, or alloantigen [22, 23].

1.5 Mutagenicity

According to a comprehensive assessment by the US National Toxicology Program, Δ^9 -THC does not have mutagenic or carcinogenic effects [25]. Δ^9 -THC induced sister chromatid exchanges and cell cycle delay at

the highest dose tested in Chinese hamster ovary cells, however it did not induce chromosomal aberrations. Further, Δ^9 -THC was not mutagenic in several bacterial *Salmonella typhimurium* strains (the Ames test). Cultured human lymphocytes treated with Δ^9 -THC (up to 100 $\mu\text{g/ml}$) for 72 hours showed no induction of chromosomal abnormalities [26]. There was no increase in frequency of micronucleated erythrocytes in the blood of mice administered oral Δ^9 -THC up to 500 mg/kg for 13 weeks [25]. Oral administration of Δ^9 -THC at doses up to 50 mg/kg/day for 2 years revealed no carcinogenic effects in rats. There was more equivocal evidence for increased neoplastic activity in mice treated with 125 mg/kg/day Δ^9 -THC for 2 years due to an increased incidence of thyroid gland follicular cell adenomas. However, this was not dose-dependent, with no increased incidence of adenomas in the 250 and 500 mg/kg/day groups. These are extremely high doses: an oral 125 mg/kg Δ^9 -THC dose in mice equates to a 625 mg Δ^9 -THC dose in a 60 kg human (the maximum recommended daily dose of dronabinol is 144 mg in a 60 kg human) [2].

1.6 Fertility and teratogenesis

Oral administration of Δ^9 -THC in rats (5-25 mg/kg/day) for 77 days reduced the size of the seminal vesicles and seminal fluid volume [2]. Δ^9 -THC also decreased spermatogenesis and the number of Leydig cells in the testis. However, sperm count, mating success and testosterone levels were not affected. More recently Δ^9 -THC reduced mouse sperm motility, and a 50 mg/kg dose administered to male mice before mating reduced litter sizes by 20% [27].

Pure Δ^9 -THC (dronabinol) use is restricted to a small number of therapeutic applications in humans and epidemiological and pharmacovigilance data do not exist with which to assess its teratogenicity in humans. Δ^9 -THC readily crosses the placenta into the blood of the foetus and is secreted in maternal milk during lactation [28-30]. *In vitro* Δ^9 -THC reduces the cell turnover of human trophoblasts, the major placental cells [31]. Numerous animal teratogenicity studies were conducted in the 1970's which collectively suggest that Δ^9 -THC exposure (at doses up to 400 mg/kg) during gestation may promote subtle reductions in foetal weights and litter numbers, but with no gross physical abnormalities observed [32-35]. Exposure of pregnant animals to Δ^9 -THC can affect offspring neurobehavioral development with effects reported on altered locomotor activity, cognitive dysfunction, and vulnerability to drugs of abuse [36-38].

1.7 DUID

Oral Δ^9 -THC (dronabinol) is reported to cause driving impairment in both driving simulator and on-road [39-41]. At 10 and 20 mg doses, dronabinol increased standard deviation of lateral position (SDLP), indicative of

loss of road tracking control, and time to speed adaptation, indicative of increased reaction times in response to a followed vehicle [39]. The impairments were dose-dependent and were observed in occasional and heavy users of cannabis, although effects appeared greater in the occasional users. 25% of the heavy users displayed comparable or worse impairments than those observed at a 0.05 % blood alcohol concentration (BAC).

2. Adverse reactions in humans

Δ^9 -THC has very similar pharmacological and subjective effects to cannabis in humans. Users may experience euphoria, laughter and increased loquacity. Δ^9 -THC increases appetite, promotes dry mouth and occasional dizziness, and enhances visual, olfactory and auditory perceptions. THC exposure may also cause nausea and vomiting in some users [42]. Δ^9 -THC's effects are mostly subject to tolerance with repeated exposure.

Δ^9 -THC exposure can cause subtle cognitive deficits such as impaired attention and short-term memory impairment [43]. Higher doses of Δ^9 -THC are associated with anxiety, panic, confusion, and disorientation in some users. Δ^9 -THC exposure can provoke transient psychosis-like psychological phenomena in some healthy participants [44, 45]. For example, Sherif et al. (2016) showed that intravenous Δ^9 -THC increased conceptual disorganization, fragmented thinking, suspiciousness, paranoid and grandiose delusions, and perceptual distortions [46]. However, these effects were modest in magnitude and reversible. In one study of 22 participants, any psychosis-related effects completely resolved and did not prompt hospitalisation [44]. Although, one participant was administered a benzodiazepine to manage their psychological distress.

RCTs in which Δ^9 -THC has been sometimes given daily to participants for periods of years, generally report low to moderate toxicity and a low incidence of serious adverse events. One of the largest and longest running trials to date assessed the efficacy of daily, oral Δ^9 -THC administration (up to 28 mg/day) for 3 years in multiple sclerosis patients. Δ^9 -THC was generally well tolerated in the 329 patients receiving the drug [47] with no difference in the median number of adverse events in the placebo group and Δ^9 -THC group. Δ^9 -THC-treated patients experienced more dizziness and light-headedness (32% THC group versus 7% in the placebo group), and dissociative thinking or perception disorders (30% Δ^9 -THC group versus 4% in the placebo group). Δ^9 -THC-treated patients experienced less musculoskeletal pain and aches (15% versus 25% in the placebo group). While there was no greater rate of serious adverse events in the Δ^9 -THC group relative to placebo, more participants in the Δ^9 -THC group discontinued the trial relative to the placebo group (43% in the Δ^9 -THC group versus 24% in the placebo group).

Similar results were observed in another shorter duration trial of 14 weeks in multiple sclerosis patients who received daily oral Δ^9 -THC doses of up to 25 mg per day (there were 206 people in the Δ^9 -THC group)

[48]. Δ^9 -THC-treated patients were more likely to experience dry mouth (26% in the Δ^9 -THC group versus 7% in the placebo group). Diarrhoea was more common in the Δ^9 -THC group than the placebo group.

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