WHO Expert Committee on Drug Dependence Pre-Review

Extracts and tinctures of cannabis

Section 3: Toxicology

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization
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Contents

1. Toxicology .............................................................................................................. 5
   1.1 Sativex® (Nabiximols)......................................................................................... 5
   1.2 Cannabis extracts, tinctures, oils and tea............................................................. 6

2. Adverse reactions in humans ............................................................................... 9
   2.1 Sativex® (Nabiximols)......................................................................................... 9
   2.2 Cannabis extracts, tinctures, oils and tea ............................................................. 9
1. Toxicology

1.1 Sativex® (Nabiximols)

Sativex is a registered medicine that is essentially a tincture formulation containing Δ⁹-THC, CBD and a cannabis-extracted botanical drug substance (BDS), that is solubilised in ethanol and propylene glycol. A 100 µl spray of Sativex contains 2.7 mg Δ⁹-THC and 2.5 mg CBD which is applied to oromucosal membranes. It is recommended that a maximum of 12 sprays are administered per day (giving a total daily dose of 32.4 mg of Δ⁹-THC and 30 mg of CBD).

Like Δ⁹-THC and cannabis (see Reports 1 and 3), Sativex may transiently increase heart rate and blood pressure early in therapy. Following Sativex dosing in healthy volunteers up to 18 sprays twice daily, there were no clinically relevant changes in heart rate, blood pressure or QT, PR or QRS interval duration [1].

Sativex does not appear to be mutagenic or carcinogenic. Sativex was not mutagenic in several Salmonella typhimurium and Escherichia coli strains in the Ames test [1]. Nor did it lead to chromosome disruptions of breakages in vivo in mice and rats in the micronucleus tests, or in rat hepatocytes in the unscheduled DNA synthesis assay [1]. Sativex did not promote genotoxicity in a forward mutation assay in mouse L5178Y cells [1]. The US National Toxicology Program has shown that Δ⁹-THC does not have mutagenic or carcinogenic effects (also see Report 3) [2]. As these data were available with Δ⁹-THC, GW Pharmaceuticals conducted a long-term carcinogenicity study in rats with a CBD-rich cannabis extract otherwise known as CBD BDS [1]. Rats received oral doses of 5-50 mg/kg/day of CBD BDS which revealed no carcinogenic effects.

Treatment of rats with a 1:1 Δ⁹-THC BDS and CBD BDS mixture did not affect fertility at doses up to 12.5 mg/kg/day of Δ⁹-THC and CBD, a dose greatly exceeding the maximal dose recommended in humans [1]. Publicly available data do not exist on the impact of Sativex on male fertility (please also see Report 1 and 3). There is no relevant publicly available data on the effects of Sativex on human reproduction. There was no evidence for teratogenicity in rats and rabbits treated with oral doses of a 1:1 Δ⁹-THC BDS and CBD BDS mixture up to 12.5 mg/kg/day of each active component [1]. The highest dose was reported to have maternal toxicity in rabbits but the specific nature of this toxicity was not described [1]. Foetal weights and impaired skeletal ossification was observed in rabbits following the highest doses of the 1:1 Δ⁹-THC BDS and CBD BDS mixture that was tested.
Rats orally administered 4 mg/kg/day of a 1:1 Δ⁹-THC BDS and CBD BDS mixture from the time of fertilisation to weaning resulted in a lower body weight gain and slightly impaired righting reflex in the offspring [1], however this dose would exceed the equivalent maximum daily dose in humans that is recommended by the manufacturer. Following oral administration of a 1:1 mixture of Δ⁹-THC BDS and CBD BDS, high concentrations of Δ⁹-THC and CBD were measured in the breast milk of lactating rats [1]. Oral administration of 1:1 Δ⁹-THC:CBD BDS from the time of fertilisation to weaning impaired nursing behaviour and pup survival at doses of greater than 5 mg/kg/day [1].

The effects of Sativex on driving performance in a driving simulator or in an on-road test has not been assessed. It was shown to have no effect on driving-related ability in 33 multiple sclerosis patients using the Vienna test system, which is a series of cognitive tests that evaluate visual pursuit, reaction time, stress reactivity and traffic perception [3]. This study was not placebo-controlled and compared driving ability to baseline performance after 4-6 weeks of daily Sativex treatment (5 sprays per day).

1.2 Cannabis extracts, tinctures, oils and tea

Very little information exists on the toxicology of cannabis extracts, tinctures, oils and tea. Some toxicity data suggests that the toxicity of pure Δ⁹-THC does not differ to that of a full-spectrum cannabis extract rich in Δ⁹-THC that also contains relatively low concentrations of other plant components such as cannabinoids, terpenoids, and flavonoids. For example, one study compared the effects of Δ⁹-THC and a cannabis extract matched for Δ⁹-THC content on rate of resorptions in pregnant mice [4]. It showed that both Δ⁹-THC and the cannabis extract equivalently increased the rate of resorptions, and so the additional compounds in the cannabis extract did not modify the actions of Δ⁹-THC. There are other data suggesting that CBD may modulate the effects of Δ⁹-THC, and that increasing CBD content in Δ⁹-THC-rich cannabis may reduce the adverse dose-related psychopharmacological effects of Δ⁹-THC [5]. Clearly more research is needed to examine whether other plant components found in cannabis extracts modulate the toxicological effects of Δ⁹-THC, or whether the extracts themselves have unique toxicity.

The production of cannabis concentrates has proliferated in recent times with the rise of legal recreational and medicinal cannabis. There are several methods for producing concentrates: 1) dry processes to produce kief or finger hash; 2) water-based methods to make hashish, bubble and ice wax; 3) CO₂ extraction to produce CO₂ oils; and 4) solvent-based methods to produce...
isopropanol oil, butane hash oil, Rick Simpson oil, honey oil, honeycomb, wax, and shatter [6]. The latter solvent-based methods have arisen in the unregulated recreational and medicinal cannabis milieu of the US, and contain up to 80% $\Delta^9$-THC, unlike cannabis flower which often contains 15% $\Delta^9$-THC content [7]. The solvents used can be accessed easily at low cost and include naptha, isopropanol, acetone, hexane, ethyl alcohol and butane. One of the potential health issues associated with the use of these preparations is that they may contain residual solvent which is then ingested by the user. Solvent–based methods can be dangerous in an open environment and have caused disastrous fires and explosions. It is for this reason that these methods are banned in California. CO$_2$ extraction methods offer a safer alternative to solvent-based methods and are increasingly being used, however these methods require technical knowledge and more expensive infrastructure.

Another issue with the use of cannabis concentrates is that their production methods also concentrate other contaminants in the final product such as pesticides, which are prevalent in unregulated cannabis markets [8]. Indeed, 70% of pesticide contaminants are transferred to the user in cannabis smoke [8, 9]. Concentrates are being increasingly consumed using e-cigarettes and vape pens. Cannabis oils are viscous, and for them to flow easily from the cartridge to the heating element, thinning agents such as propylene glycol and polyethylene glycol 400 are often used (note: cannabis oils produced from CO$_2$ extraction are less viscous and do not require thinning agents to be used in vape pens). Unfortunately, thinning agents can produce high concentrations of toxic acetaldehyde and formaldehyde when heated in these devices [10]. In addition, terpenes found in cannabis concentrates such as myrcene can be converted to the toxic degradants methacrolein (an irritant) and benzene (a carcinogen) as a result of dabbing, a widespread method of smoking concentrated cannabis oils which involves combustion [11].

Very little information exists on the toxicology of cannabis tea, but it is likely to have insignificant toxicity when consumed appropriately. The preparation process endorsed by the Office of Medicinal Cannabis in the Netherlands involves the use of 1 g of cannabis flower and
placing it in 1 L of boiling water for 15 min [12]. This yields approximately 3.5 mg of $\Delta^9$-THC per cup which is a threshold dose for subjective effects in a naïve user [8].

Cannabis was first introduced into western medicine largely in the form of cannabis ethanolic tinctures in the 19th century [13]. Such formulations are still in use today, either as artisanal preparations or as a registered medicine in the form of Sativex. The issue with artisanal tinctures is that the exact ethanolic formulation or starting cannabis material may vary leading to inconsistent cannabinoid content [13]. Other than that, there is no evidence to suggest that cannabis tinctures have any unique toxicity above and beyond that observed with $\Delta^9$-THC-rich cannabis and $\Delta^9$-THC alone.

Hemp seed oils are unlikely to have any significant toxicity and are accepted as foods and animal feed in many countries around the world with strict caps on low concentrations of $\Delta^9$-THC (e.g. 10 $\mu$g of $\Delta^9$-THC/gram of hemp seeds (10 ppm)) [14]. The oil is rich in various nutrients such as polyunsaturated fatty acids (PUFAs) such as omega-3 and 6 fatty acids, and a broad range of vitamins and minerals. Hemp seed oils theoretically should not contain significant cannabinoid content, as the seed has low concentrations of cannabinoids - the seed of hemp-type and drug-type cannabis contains no greater than 0.5 and 2 $\mu$g of $\Delta^9$-THC per g of seeds respectively [14, 15]. However, suboptimal manufacturing processes invariably lead to contamination with $\Delta^9$-THC, mainly due to the hull being incompletely removed from the seed and the seed being inadequately washed [16-18]. There is one suspected case of a cannabinoid poisoning in a child who consumed hemp seed oil, however the amount of $\Delta^9$-THC in the product was very low [16].
2. Adverse reactions in humans

2.1 Sativex® (Nabiximols)

In the Australian Therapeutic Goods Administration’s product information sheet the percentage of patients experiencing specific adverse events was outlined in 805 Sativex-treated participants and 741 placebo participants [19]. Overall there was a higher number of participants reporting adverse effects in the Sativex group (66%) than the placebo group (45%). The most commonly reported adverse reactions observed were dizziness (24.8 % in the Sativex group versus 7% in the placebo group) and fatigue (11.1 % in Sativex group versus 6.6% in the placebo group). These reactions were usually mild to moderate and resolved within days of treatment [20]. As Sativex is an oromucosal spray, rare instances have been reported of pain and discomfort, as well as distorted taste, mouth ulceration and glossodynia (burning sensation in the mouth and tongue) [20]. Like with Δ⁹-THC and cannabis, serious psychiatric adverse events may occur in some patients. Psychiatric adverse events observed in clinical trials included: disorientation (Sativex 4.0% versus placebo 0.5%); depression (Sativex 1.9% versus placebo 0.8%); euphoria (Sativex 2.2% versus placebo 0.9%); and dissociation (Sativex 1.7% versus placebo 0.1%). In one study in healthy participants given 18 sprays of Sativex twice daily, 4 out of 41 experienced a transient psychotic reaction [1].

2.2 Cannabis extracts, tinctures, oils and tea

The adverse reactions produced by Δ⁹-THC-rich cannabis extracts, tinctures, oils and tea in humans are likely to be similar to those observed with Δ⁹-THC-rich cannabis and Δ⁹-THC (see Report 1 and 3). The abuse of cannabis oils for recreational purposes is an increasing concern given our knowledge that cannabinoid toxicity, like for all drugs, is dose-dependent. Acute exposure to higher Δ⁹-THC doses may increase the likelihood of tachycardia, orthostatic hypotension, fainting and drug-induced psychotic reactions [8, 21-23]. A cross-sectional survey of 83,867 cannabis users showed that use of butane hash oil engendered greater restlessness, anxiety, memory impairment, and was less pleasurable than use of cannabis flower [24].
3. References

1. Sativex, in MIMS Online 2018, Medi Media.: St Leonards, NSW.
