



WHO Expert Committee on Drug Dependence Pre-Review:

Cannabis plant and resin

Expert Peer Review 2

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential: Only a few animal studies have involved actual marijuana (cannabis plant) smoke and demonstrated exposed animals exhibited withdrawal through cessation or precipitation by a CB₁ receptor antagonist. Withdrawal effects were dose dependently resolved by intravenous delta-9-THC but not marijuana smoke. Commentary surrounding the studies included rhesus monkeys may have exhibited withdrawal symptoms due to disruption of the routine as opposed to being a result of abrupt cessation. The Pre-Review report also highlights that comparatively low percentage amounts of delta-9-THC were present in the marijuana used compared to percentage amounts seen in seized marijuana. In humans, the Pre-Review report states that cannabis dependence is characterized by the development of withdrawal symptoms upon abstinence from regular use (occurring typically within 1 to 2 days) with multiple lines of evidence (encompassing laboratory studies in inpatients, ecological momentary assessment and self-report investigations in outpatients and structured online surveys) converging to confirm and characterize a cannabis withdrawal syndrome. Stated symptoms 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. Psychological symptoms predominate, with peak intensity usually 2 to 6 days after last use. Similar to withdrawal from other drugs of abuse (including nicotine), maximal discomfort lasts 2 to 3 weeks with gradual return to baseline, although disruption of sleep may linger. The Pre-Review cites that while dependence may develop with regular use of cannabis of low percentage amount, regular use of high percentage amount cannabis is associated with enhanced

severity of withdrawal symptoms as well as with increased risk memory impairment and paranoia.

Overall, available data with many studies in humans demonstrate that the cannabis plant has dependence potential which also incorporates cannabis resin given the similar constituent cannabinoids and non-cannabinoid chemicals.

Abuse potential: Only a few animal studies have involved actual marijuana (cannabis plant) smoke and demonstrated an abuse potential through initial increases and then longer decreases in hyperactivity and locomotor activity with decreased rearing also being observed (reversible by a CB₁ receptor antagonist). In mice, inhalation of higher percentage amount delta-9-THC cannabis smoke produced characteristic cannabinoid effects of anti-nociception, catalepsy and hypothermia. In humans, cannabis is one of the most used drugs of abuse in the world. The Pre-Review report states the reinforcing effects of smoked cannabis have been demonstrated in a number of laboratory-based self-administration procedures with smoked cannabis being readily self-administered by experienced users. In these studies, participants chose to smoke cannabis cigarettes (delta-9-THC content ranging from 1.8 to 5.8%) rather than placebo cigarettes in choice procedures and preferred higher doses over lower doses within this range (the range itself being somewhat lower than reported in seized cannabis plant/resin material). Drug discrimination studies have also demonstrated participants readily differentiated between cannabis smoke and non-cannabis smoke. Self-reported subjective effects associated with smoked cannabis in laboratory studies include dose-dependent increases in ratings of “drug effect,” “high” or “stoned”, similar to effects produced by delta-9-THC alone.

Overall, available data regarding the use of cannabis (plant and resin) and laboratory studies (primarily in humans) have demonstrated cannabis plant and resin exhibit a significant abuse potential.

b. Risks to individual and society because of misuse

Cannabis plant and its resin are widely used around the world. The Pre-Review report describes cannabis consumption causing euphoria, laughter and talkativeness. It is an appetite stimulant and may promote dry mouth, dizziness and increases in visual, olfactory and auditory perceptions. Time perception may be altered and some users may experience anxiety and panic reactions. Cannabis intoxication can impair attention and short-term memory function and can precipitate psychotic reactions in vulnerable individuals. The Pre-Review report also

cites several recent case reports of young children accidentally ingesting cannabis and undergoing respiratory depression, tachycardia and temporary coma.

Whilst the Pre-Review report states that cannabis is not associated with acute fatal “overdoses”, this is controversial and a recent consensus report by the National Academies of Science, Engineering and Medicine (NASEM) concluded that there is insufficient evidence to support or refute associations between cannabis use and increased risk of all-cause mortality and overdose lethality in humans. Of toxicological concern is the effect of cannabis on the cardiovascular system and the Pre-Review report cites that cannabis acutely increases heart rate and blood pressure in humans but there is an uncertain association between cannabis use and heart attack. There is some limited population evidence to suggest that smoking cannabis increases the risk of ischaemic stroke. Aside from cardiovascular effects, regular cannabis users may experience higher rates of chronic bronchitis. Acute cannabis use impairs certain types of cognitive function and can interfere with attention, learning and memory. The Pre-Review report mentions there are frequent reports of acute cannabis intoxication precipitating a short-lasting psychotic state which reverses once the effects of the drug have abated. Human population studies have linked cannabis use to schizophrenia, with cannabis increasing the risk of developing the disorder in a dose-dependent manner, where heavier cannabis use increases the risk of developing schizophrenia and that adolescent cannabis use may bring forward the age of schizophrenia onset. The Pre-Review report states that it is contentious however whether cannabis actually causes schizophrenia. The NASEM report on cannabis noted moderate evidence for cannabis use increasing: manic symptoms in bipolar disorder patients; a small increased risk of developing depression; suicidal ideation, suicide attempts and completions in heavy users; and, the development of social anxiety disorders.

The Pre-Review report outlines studies (although there are many more) showing cannabis can cause driving impairment and that people driving under the influence of cannabis are more likely to be involved in a car accident, although the level of risk is generally not as great as with alcohol. The Pre-Review report states that some studies suggest that drivers under the influence of cannabis drive more slowly, make fewer attempts to overtake, and leave greater distances between themselves and the vehicle in front. However, other studies show that cannabis use impairs reaction time, lane control, speedometer monitoring, hand and body steadiness, braking stop time and promotes inappropriate responses in an emergency scenario.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

The Pre-Review report refers to the World Drug Report 2017 which states that more than 183 million adults are estimated to have used cannabis in 2015 (lower estimate: 128 million; upper estimate: 238 million), with about the same absolute number of users (~50 million) in Africa, the Americas and Asia compared to ~28 million in Europe. In terms of prevalence for the 15-64 age group, estimates are highest for North America and West and Central Africa, followed by Oceania. The estimated global prevalence of cannabis use in the general population (15-64 age group) ranged from 2.7 to 4.9% with an increasing upward trend. The Pre-Review report also cites from the World Drug Report 2017 that cannabis continues to be the most widely illicitly produced drug worldwide, cultivated in 135 countries covering 92% of global population with most of the production being for herbal cannabis. In 2014 and 2015, the amount of cannabis resin seized was reportedly about 1,500 tons and the amount of cannabis herb seized was just over 7,000 tons. The trafficking of cannabis seems to have stabilized at a high level over the past decade (compared with the level in the late 1990s), with currently most seizures taking place in North America but with various trends being noted in other regions (e.g. doubling in seizures in the period 2010-2015 in Africa and South America).

d. Need of the substance for medical (including veterinary) practice

Therapeutic use of delta-9-THC appears to be restricted to the stereochemical variant (-)-*trans*-delta-9-THC (dronabinol). Dronabinol marketed as Marinol® has approval in the United States of America for the treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatment. Dronabinol is either approved or available under 'special access rules' in the United Kingdom, Scandinavian countries, and most Western European countries. For example, it is approved in Austria, Denmark and Ireland for CINV unresponsive to conventional treatment in oncology and palliative care and for cancer pain in Denmark. In Ireland, dronabinol is approved for appetite stimulation in HIV. Dronabinol can be prescribed for any type of chronic pain and for any condition in palliative care in Germany. delta-9-THC has also been studied for other indications, including; abdominal pain, dementia, multiple sclerosis, neuropathic pain and for nausea and vomiting.

e. Need of the substance for other purposes (e.g. industrial)

The Pre-Review report states that low percentage content delta-9-THC cannabis (hemp) for industrial use is undertaken under controlled circumstances. In European and North American countries, to be legally classified as hemp the crop may not contain more than 0.2% or 0.3% of delta-9-THC, respectively. While national regulations vary, such cultivation is ongoing in several countries, to produce paper, paper, textiles, rope or twine, and construction materials based on fiber from stalks. Grain from industrial hemp is used in food products, cosmetics, plastics and fuel.

f. Measures taken by countries to curb misuse

No information provided in the Pre-Review report.

g. Impact if this substance is scheduled

No specific information. Cannabis (as defined) and cannabis resin are currently listed as Schedule I and IV substances in the 1961 Single Convention on Narcotic Drugs. Cannabis and cannabis resin are not listed on the WHO Model List of Essential Medicines.

2. Are there absent data that would be determinative for scheduling?

Cannabis (as defined) and cannabis resin are currently listed as Schedule I and IV substances in the 1961 Single Convention on Narcotic Drugs. The Convention states that a drug be placed in Schedule IV if a drug in Schedule I is particularly liable to abuse and to produce ill effects and that such liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV. Whilst the Pre-Review report provides information pertaining to these aspects, further data may be required in assessing therapeutic advantages. The Pre-Review report does omit some detail and various studies, in particular those in relation to drug driving and fatal case reports.

3. Other comments or opinions

It should be noted that (-)-*trans*-delta-9-THC (dronabinol) is cited as being the primary psychoactive substance in botanical cannabis. Therefore, due to the nature of the substance with delta-9-THC being an active component of the cannabis plant and associated products, it is important to separate out the data involving cannabis (as defined) and cannabis resin only and the Pre-Review report has achieved this.