

WHO Expert Committee on Drug Dependence Pre-Review:

Cannabis plant and resin

Expert Peer Review 1

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential: Rimonabant-precipitated withdrawal indicative of physical dependence has been reported in mice and rats and these effects in mice are reversible by intravenous Δ^9 -THC administration but not by smoke exposure. Spontaneous withdrawal has not been evaluated. Exposure to cannabis smoke for one year (once a day or once every two days) in rhesus monkeys suppressed increases in progressive ratio performance maintained by food but did not result in abstinence effects indicative of dependence.

The review indicates that "Estimated percentage of regular cannabis users who have experienced at least one episode of cannabis withdrawal during abstinence (e.g., when trying to quit) range from 16 to 33%..." It also describes that "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. Psychological symptoms predominate, with peak intensity usually 2 to 6 days after last use".

Abuse potential: The pre-review identifies limitations in preclinical research to date as not often using the clinical route of administration and typically using Δ^9 -THC as a proxy for cannabis. Mice exposed to cannabis smoke display cannabinoid-like tetrad effects (catalepsy, antinociception, hypothermia, hypolocomotion) that can be attenuated by rimonabant (providing evidence that at least some of its effects are CB₁ receptor mediated).

In controlled, laboratory studies, experienced cannabis users readily smoke cannabis and would choose higher over lower doses. Self-reported subjective effects

associated with smoked cannabis in laboratory studies include dose-dependent increases in ratings of “drug effect,” “high” or “stoned.” The pre-review indicates that, similar effects are produced by Δ^9 -THC alone when administered orally or when smoked, and that these results suggest that the cannabis constituent responsible for the plant’s reinforcing effects is Δ^9 -THC. " The peer-reviewer is cautious regarding this conclusion, however, in that just because THC can produce these subjective effects, it does not necessarily mean other constituents of cannabis could not also do so.

b. Risks to individual and society because of misuse

Preclinical studies suggest that the lethal dose is not likely obtainable by humans. Cardiovascular effects of cannabis appear minimal or transient. Initial ingestion acutely promotes tachycardia and increased supine blood pressure that subsides with tolerance and may even result in opposite effects. Cannabis smoking acutely improves airway dynamics and forced expiratory capacity due to the bronchodilatory effects of Δ^9 -THC, and "moderately strong epidemiological evidence" indicates that cannabis use does not increase the risk of cancers of the lung, head and neck.

Short-term (acute) effects such as cognitive effects include impaired short-term memory, altered judgment and impaired motor coordination. Several reports indicate acute cannabis intoxication can precipitate a short-lasting psychotic state which reverses once the effects of the drug have abated. However, the argument that cannabis can cause schizophrenia appears contentious as the pre-review indicates, "The argument that cannabis causes schizophrenia is contentious, however, as some have observed that sharp increases in global cannabis use in recent decades has not increased the incidence of schizophrenia.", and that "The vast majority of people who use cannabis will never develop a psychotic disorder, and those who do likely have some genetic vulnerability to cannabis-induced psychosis." The pre-review reports that a recent systematic review and meta-analysis of 69 cross-sectional studies and 2,152 cannabis users and 6,575 controls found only a small effect size for reduced cognitive functioning in frequent or heavy cannabis users. The pre-review also indicates that "...no association between cannabis use and reduced cognitive function could be found in studies with a greater than 72 hour abstinence period, suggesting that the effects of cannabis use on cognition were reversible." Cannabis use can impair driving, and the pre-review (Toxicology) reports that it can cause a low to moderate increase in the risk of accident of from 20-30%.

Maternal cannabis users give birth to babies with on average 109 g lower birth weights than non-cannabis using mothers. Impaired brain development as demonstrated by poor connectivity may contribute to the association between early, regular cannabis use and a decline in IQ, although the extent of these cognitive difficulties appears equivocal. Cannabis smoking has been reported to increase the risk of testicular cancer by 2.5-fold. There is the risk that when children consume cannabis possible

respiratory depression, tachycardia and coma may ensue. Other, minor toxicological effects of cannabis were noted in the pre-review.

The estimates of the risk of developing cannabis use disorder among users appear to vary among studies and countries, but it appears that 1 in 10 or 1 in 11 is representative. However, the pre-review warns, "the global epidemiological data based for prevalence of cannabis use and cannabis use disorders is surprisingly small, and de facto too small to report reliable trends;" and "...the data seem inconsistent:"

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

The pre-review indicates the nonmedical prevalence of cannabis use is global, with an estimate of more than 183 million adults having used cannabis in 2015 alone and constitutes a global prevalence of 3.8%. Regional trends in use can be contrary to global trends, and prevalence can vary widely across countries from less than 1% to over 38% as indicated in a provided table. Although the prevalence of cannabis use is higher in men than in women, the gap is narrowing with time. THC content is increasing globally, and the potency of retail cannabis (legalized) in 2015–2016 is 10–20% higher than the THC content found in seized illegal cannabis in 2010.

Regarding the global impact of cannabis use, the pre-review indicates that the burden of disease attributable to cannabis use disorder, expressed in disability-adjusted life years (DALYs) (one DALY represents one year of life lost either due to premature mortality or due to living with disability) was 646,480 DALYs in 2016.

Regarding the illicit production of cannabis, the pre-review indicates that cannabis is the most widely illicitly produced drug worldwide, cultivated in 135 countries covering 92% of global population, and most of this production is for herbal cannabis. Cannabis seizures made up 53% of all drug seizures worldwide 2015, and almost two-thirds (64 percent) of the total quantity of global cannabis herb seized was seized in the Americas.

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

Neither cannabis nor cannabis oil are listed in the WHO Model List of Essential Medicines. The pre-review (Epidemiology) indicates that as of November 2017 medical cannabis can be used legally in Australia, Canada, Chile, Colombia, Germany, Israel, Jamaica, The Netherlands, Peru, and in 29 US states. It has been used for a number of conditions, as diverse as worm infestations, to relieving pain. The pre-review indicates that many studies report subjective perceptions of symptom relief with HIV, arthritis, neoplasms, neuropathy, psychosis, depression, multiple sclerosis, cluster headaches, cancer and other chronic pain. Prevalence use figures in these clinical populations are markedly above the rate of cannabis use in the general adult population.

The "Therapeutic Applications" pre-review provides detail regarding the therapeutic applications of cannabis. In one survey, the top five medical conditions for which cannabinoids were employed as treatment were back pain, sleep disorders, depression, post-injury pain, and multiple sclerosis. Several member states have medicinal cannabis laws in place and in which cannabis can be obtained for medical reasons including Canada, The Netherlands, Israel, Australia, Argentina, Austria, Chile, Colombia, the Czech Republic, Denmark, Germany, Guam, Portugal, Puerto Rico, Italy, Uruguay, and Jamaica. Cannabis is illegal and not approved at the federal level for medicinal applications in the U.S.A., although 29 states and the District of Columbia have medicinal laws in place.

The pre-review found varied efficacy of cannabis for a variety of clinical ailments when limited to randomized clinical trials. In a trial of 67 participants with HIV infection, dronabinol and smoked cannabis produced significantly greater weight gain than placebo and were found safe. Multiple randomized, controlled clinical trials show cannabis as an effective analgesic although most of these used plant-derived cannabinoids. Importantly, a placebo-controlled trial of inhaled aerosolized cannabis demonstrated a dose-dependent reduction in spontaneous pain ratings in diabetic patients suffering from peripheral neuropathy that had been treatment-refractory. Three randomized controlled trials have shown smoked cannabis to be an effective treatment for neuropathic pain. Two open-labeled, uncontrolled, observational studies of smoked cannabis or vaporized cannabis reported significantly decreased motor disability and pain scores in Parkinson's patients.

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

Low potency (0.2% to 0.3% Δ^9 -THC) cannabis (hemp) is cultivated to produce 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

This topic appears not to be addressed in the component pre-reviews. At the time of this peer review (20180521), the Annex was not available for evaluation in this regard.

g. Impact if this substance is scheduled

The impact of continued scheduling of cannabis was not addressed in any of the component pre-reviews.

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

It would be helpful in a future expanded review of cannabis to have comparisons of cannabis effects and abuse and its related disorders with synthetic cannabinoid effects and abuse and their related disorders. Although cannabis is currently scheduled within The Single Convention on Narcotic Drugs, 1961, and the synthetic cannabinoids have been scheduled in recent years in The Convention on Psychotropic Substances, 1971, to obtain a more holistic vision of the possibilities how cannabis should be controlled or not it would be informative to have these comparisons.

3. Other comments or opinions

Important information contained in the therapeutic pre-review regarded the reference to one placebo-controlled trial that demonstrated the utility of aerosolized cannabis for reducing spontaneous pain ratings in diabetic peripheral neuropathy patients that were treatment-refractory (for pain). It would be helpful in a future expanded review to provide more details of this study because it is important to understand whether cannabis can be an effective medical treatment in situations where all other drugs have failed.

Considering that there are over 500 compounds within the cannabis plant, it would be useful in a future review to document why the common assumption is made that Δ^9 -THC is the primary psychoactive constituent in cannabis. Reference is made to the Mechoulam and Gaoni 1967 report to support this assumption, but additional documentation is desired to complement that study to fully support this assumption.