WHO Expert Committee on Drug Dependence Pre-Review

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Cannabis plant and cannabis resin

Section 4: Therapeutic use

World Health Organization

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. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

1.1 Extent of therapeutic use and epidemiology of medical use

It is estimated that between 3% and 5% of the world's population has tried cannabis for nonmedical reasons *(1)*. Among users of medicinal cannabis, an international survey of 953 participants from 31 countries found that most were current users under the care of a health professional and had been using cannabis-based medications for several years. Most had experience with herbal products (administered by smoking) before the onset of their medical conditions, or after onset but prior to a physician's recommendation for cannabis therapy. The survey found that the five medical conditions for which cannabinoids were most often used as treatment were back pain, sleep disorders, depression, post-injury pain and multiple sclerosis *(2).*

A literature review on cannabis use recommended by physicians reported a prevalence ranging from < 1.7% among Israeli cancer patients to 17.4% in the USA for a range of conditions, pain being the most common. Among those who reported self-medicating, a range from 15% in Canadian patients with chronic pain to 30% in British patients with multiple sclerosis was noted. Pain, sleep disturbances and anxiety were the most common reasons given for cannabis use *(3).* Two studies have noted that there are no significant demographic differences between adults who use medicinal cannabis and those who use cannabis recreationally, although in an adjusted analysis one study found that medicinal cannabis users had higher daily cannabis use, were more likely to be in poorer health, and had lower levels of both alcohol use disorders and non-cannabis drug use *(4).*

As of April 2018, 29 states in the USA as well as the District of Columbia (DC), and the territories of Guam and Puerto Rico had laws on medicinal cannabis in place, although cannabis for any use remains illegal at the federal level. These states and territories stipulate, in aggregate, more than 50 different conditions for which a physician may certify or approve a patient for medicinal cannabis use. There are an estimated 2 254 782 patients using medical cannabis in the USA. In a review of data based on 96 100 adults aged 18 years and older who participated in the 2013–2014 US National Survey on Drug Use and Health, 0.8% (95% confidence interval (CI), 0.7–

0.9%) of this population used cannabis for medical purposes only. Of medicinal cannabis users, 78.8% (95% CI, 75.7–81.9%) lived in states where medicinal cannabis was legal *(5).* In the USA, approximately one in eight users of cannabis consider their use to be treatment for a medical issue *(1).*

Canada has had medicinal cannabis laws in place since 2001 and from April to July 2017, there were 201 398 registered medical cannabis clients in Canada *(6).* The Netherlands legalized medicinal cannabis in 2003. From 2011 to 2016, 95 022 prescriptions were dispensed there *(7).*

Israel legalized medicinal cannabis in the early 1990s. Up to October 2017, more than 32 000 patients had been authorized to use the product *(8).* Australia has had medicinal cannabis laws in place since 2013, Argentina since 2017, Austria since 2008, Chile and Colombia since 2015, the Czech Republic since 2012, Denmark since 2011, Germany and Portugal since 2017, Italy and Uruguay since 2013and Jamaica, since 2015.

Barriers to medicinal use in the USA include the reticence of physicians to recommend it. Reasons for this include: the lack of high-quality scientific data, physicians' concerns about physical and mental health risks of cannabis, cannabis's Schedule I Drug Enforcement Agency status, its lack of approval by the Food and Drug Administration, and physicians' resulting fear of losing their medical licences). Other barriers to use are that health care institutions direct their physicians not to certify patients due to legal status or other reasons, and the lack of insurance coverage for the drug *(9).* Barriers to research in the USA include the difficulty of navigating through several federal agencies as well as research ethics boards and local and state oversight concerns. There are also issues related to quality, quantity, and kind of product available from the current single federal source of cannabis for research use and the lack of adequate funding sources.

The European Medicines Agency has stated that the use of cannabis as a medicine must follow the laws of each Member State. European countries control cannabis under the United Nations drug control conventions, which do permit, to a certain extent, the use of drugs for medical and scientific purposes. The laws of the European Union Member States are not harmonized regarding medicinal cannabis use.

There are also challenges in research design *(10).* Controlling for the placebo effect is difficult due to the characteristic odour and taste of cannabis; this issue can sometimes be managed by using routes of administration such as injections or coated capsules. The differing effects of cannabis due to varied absorption processes have to be considered *(11).* Study participants' expectations, however, cannot be overcome as easily. In addition, ensuring that study participants do not use cannabis obtained outside the study (whether licitly or illicitly, and regardless of cohort (test or control group) assignment) is not always possible.

1.2 Effectiveness of therapeutic use

(See Table 4.1)

1.2.1 Appetite stimulation in HIV/AIDS infection

In a randomized, double-blind, placebo-controlled trial of 67 participants with HIV infection, both dronabinol and smoked cannabis led to significantly greater weight gain than administration of a placebo. This safety study also showed that both dronabinol and smoked cannabis were safe in this population and did not adversely affect viral load in comparison to placebo *(12).*

1.2.2 Autism

There have been no randomized, double-blind, placebo-controlled trials of cannabis or cannabinoids as pharmacotherapy for autism.

1.2.3 Chronic pain

Results from investigations evaluating cannabis pharmacotherapy for pain demonstrate the complex effects of cannabis-related analgesia. Many randomized, controlled clinical trials have shown cannabis to be an effective analgesic *(13).* Most of these studies, however, focused on testing the effects of plant-derived cannabinoids. In the meta-analysis by Whiting et al. (2015), for example, only 5 of the 28 trials assessed the effects of vaporized or smoked cannabis plant flower *(14).*

No randomized, placebo-controlled trials of cannabis for treatment of chronic pain have been published. One recent study, not included in the meta-analysis by Whiting et al., was a placebo-controlled trial of inhaled aerosolized cannabis, which demonstrated a dose-dependent

reduction in diabetic peripheral neuropathy spontaneous pain ratings among patients with treatment-refractory pain *(14).* More recently, Wilsey et al. conducted a randomized, placebo-controlled crossover trial of vaporized cannabis among 42 participants with central neuropathic pain related to spinal cord injury and disease *(15).* The results indicated that vaporized cannabis reduced neuropathic pain according to the rating scale, but there was no evidence of a dose-dependent effect. These authors concluded that additional research is needed to examine how interactions among cannabinoids may influence analgesic responses.

A large prospective cohort study evaluated the safety of cannabis administered by smoking, oral consumption, or vaporization and found an increase in adverse events in the group who used cannabis compared to the control group of chronic pain patients who did not use cannabis. There was no difference in the occurrence of serious adverse events between the two groups *(16).* A recent retrospective chart review demonstrated that cannabis improved measures of pain and quality of life *(17).*

1.2.4 Crohn disease

In the only randomized, double-blind, placebo-controlled trial of the use of smoked cannabis for patients with Crohn disease, no difference in remission, the primary outcome, was observed between users of cannabis and those given a placebo, but the cannabis smokers group had a significant response on the Crohn Disease Activity Index *(18).*

1.2.5 Diabetic neuropathy

A randomized, double-blind, placebo-controlled cross-over study in 16 patients with diabetic peripheral neuropathy who had treatment-refractory pain, assessed the short-term efficacy and tolerability of inhaled cannabis. Inhaled cannabis was found to be associated with a dose-dependent reduction in pain associated with diabetic peripheral neuropathy *(19).*

1.2.6 Epilepsy

Only the cannabinoid, cannabidiol, (which was reviewed at the ECDD meeting in November 2017) has been studied as a pharmacotherapy for epilepsy.

1.2.7 Neuropathic pain

Three randomized controlled trials have shown smoked cannabis to be an effective treatment for neuropathic pain. Ellis et al. demonstrated that cannabis reduced HIV-associated distal sensory predominant neuropathy when added to concomitant analgesic therapy *(20).* Similarly, two studies showed that smoked cannabis reduced central, peripheral and HIV-associated neuropathic pain when used as the primary pharmacotherapy *(12, 21).*

1.2.8 Migraine and cluster headaches

A preliminary investigation, which was presented at a scientific conference in 2017, found no difference between cannabis and amitriptyline for prophylaxis of cluster or migraine headaches, although the control arm might not represent optimal control therapy. In a subset of participants with a history of childhood migraine, acute administration of cannabis as abortive therapy decreased attack pain from both migraines and cluster headaches *(22).*

1.2.9 Opioid withdrawal

Despite intense interest in the effects of cannabis on opioid use disorder, especially in the USA, there have been no randomized controlled trials of cannabis for this disorder. In one observational study of patients with opioid use disorder undergoing a methadone taper, smoked cannabis did not lead to a reduction in opioid withdrawal symptoms *(23).*

1.2.10 Parkinson disease

In an open-label, uncontrolled, observational study of smoked or vaporized cannabis for the treatment of pain in 20 patients with Parkinson disease, cannabis significantly decreased motor disability and pain scores *(24).* A second open-label, uncontrolled, observational study of smoked cannabis in 22 participants with Parkinson disease reported significant improvement in total motor disability scores in the cannabis smokers *(25).*

1.2.11 Post-traumatic stress disorder

Only nabilone has been studied in a trial on patients with post-traumatic stress disorder, and that agent is not included in this pre-review.

1.2.12 Psychosis

Two studies of cannabidiol's effects on psychosis (not included in this pre-review) have been reported, but no other studies of cannabis or other cannabinoids as pharmacotherapy for psychosis are available.

1.2.13 Sleep disorder

Two studies have evaluated nabilone (not included in this pre-review) as a pharmacotherapy for sleep disorder. Nineteen other placebo-controlled studies on chronic pain and multiple sclerosis have evaluated sleep as an outcome. Two of these studies assessed smoked cannabis and found that it was more likely than a placebo to improve sleep *(26, 27).* While many patients report that cannabis improves their sleep due to its propensity to reduce sleep latency *(28),* cannabis has also been shown to reduce REM sleep in a fashion similar to alcohol *(29).* Therefore, the quality of sleep achieved with cannabis may be poor.

Table 4.1: Studies of cannabis plant and cannabis

Intervention	Administration method	Dose evaluated	Comparator	Number of studies described in this report	Indication
Cannabis	Smoking, vaporizer	3.95% THC	Placebo	1	Appetite stimulation HIV/AIDS Infection
		1–12.5% THC	Placebo or no cannabis	4	Chronic pain
		230 mg THC	Placebo	1	Crohn disease
		1–7% THC	Placebo	1	Diabetic neuropathy
		1–8% THC	Placebo	3	Neuropathic pain
		10–200 mg THC	Amitriptyline (M), verapamil (C)	1	Migraine and cluster h
		Unspecified	None – observational	1	Opioid withdrawal
		1g	None – observational	2	Parkinson disease
		2.5–9.4% THC	Placebo	2	Sleep disorder

C: cluster headache; M: migraine headache; THC; delta-9-tetrahydrocannabinol.

2. Listing on the WHO Model List of Essential Medicines

Not listed.

3. Marketing authorizations (as a medicinal product)

Bedrocan cannabis (the Netherlands) produces five standardized plant varieties (whole dried flower) for patient use, which are available to patients under direct care of a physician. The company's medicinal cannabis is available for patients in Australia, Canada, Czech Republic, Denmark, Germany, Italy and the Netherlands. There is limited patient availability in Finland, Israel, Ireland, Norway, Poland and Sweden. For research purposes, Bedrocan cannabis is available in Australia, Brazil, Canada, Czech Republic, Denmark, Finland, Germany, Israel, Italy, Macedonia, the Netherlands and Poland. Bedrocan's cannabis oil, extracted from its own plants, is currently only available in Canada, Germany and the Netherlands. In addition, five Canadian companies produce cannabis, and the following companies export cannabis: Tilray to Australia, Brazil, Chile, Croatia, Germany and New Zealand; Canopy Growth Corporation to Australia, Brazil and Germany; Aurora Cannabis to Germany; Cronos Group to Germany; and Aphria to Australia.

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Appendix 1.

4.1.1 Search methodology for therapeutic use

Published articles on the topic of medical cannabis were identified by searching electronic databases. A PubMed search was made for articles published from 1948 to April 2018, Cochrane Central Register of Controlled Trials up to 2018, and Cochrane Database of Systematic Reviews up to 2018. The search terms used included cannabis, cannabinoids and tetrahydrocannabinol. The limits used were “administration and dosage”, “therapeutic use”, “humans” and “clinical trial”. The PubMed search resulted in 647 references, the Cochrane Central Register of Controlled Trials in 663 and the Cochrane Database of Systematic Reviews search resulted in 13 references. A total of 128 articles were identified for an initial review. There were six systematic reviews selected for initial review. As a result, the main emphasis was on randomized clinical trials.