Cannabis and Cannabis Resin

Pre-Review Report

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Expert Committee on Drug Dependence

Thirty-eight Meeting

Geneva, 14 – 18 November 2016

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Preface

With this report, DrugScience provides a unique opportunity for the World Health Organization (WHO) and its Expert Committee on Drug Dependence to initiate a critical review process of cannabis and cannabis resin for their scheduling under the Single Convention on Narcotic Drugs as amended by the 1972 Protocol. The process could ultimately open the discussion on the scheduling of cannabis and cannabis resin and lead to recommendations to the Commission on Narcotic Drugs within two years.

In the eighty years since cannabis and cannabis resin were last reviewed by the Health Committee of the League of Nations in 1935, both the social context of cannabis use and the science of drug dependence have dramatically changed. Yet, cannabis and cannabis resin continue to remain under the strictest control regime possible under the Single Convention, without a valid scientific re-assessment of this decision. Cannabis and cannabis resin are listed in Schedule I and Schedule IV respectively, which means that both remain strictly prohibited worldwide.

This also means that the Committee implicitly continues to recommend that cannabis is not to be used medically despite growing evidence of medical use worldwide and despite the availability of pharmaceutical preparations with a marketing authorization in multiple countries. Many countries are struggling with the impact of the prohibition of cannabis, be it the negative impact of prohibition on society, including over-incarceration and disproportionate sentencing, or impact on drug markets (including synthetic cannabinoids) and drug use.

The current scheduling of cannabis is in marked divergence with the Convention's principle that scheduling of substances should be based on a scientific assessment by WHO. In the absence of a recent assessment, the continued prohibition of cannabis appears completely illegitimate even though it may be legal.

A scientific review by the WHO, the only authoritative global body to make such an assessment, would greatly legitimize international policies and their national implementation. A scientific assessment of cannabis and cannabis resin appears most timely given the many debates that have emerged on this issue across the world in recent years.

I trust therefore, that the Thirty-eighth Meeting of the Expert Committee on Drug Dependence will act responsibly and will adopt, on the basis of this strong Pre-Review Report, the Pre-review of Cannabis and Cannabis Resin as an agenda item.

Geneva, September 2016

Michel D. Kazatchkine
Commissioner of The Global Commission on Drug Policy; Professor of medicine; former Executive Director of the Global Fund to fight AIDS, tuberculosis and malaria.

Foreword

The WHO Expert Committee on Drug Dependence (ECDD) recommended in its 35th (2012), 36th (2014) and 37th (2015) Sessions that a Pre-review of cannabis and cannabis resin should be undertaken. However, the ECDD Secretariat, when announcing the 38th Meeting, proposed that cannabis will be on the agenda of the 38th Meeting (14 – 18 November 2016) only as "Update".

When the ECDD will meet in November 2016, it will discuss this proposed agenda, and then will decide on the final agenda (which is at the liberty of the Expert Committee). DrugScience requests the Experts to amend the proposed agenda and replace the agenda item "Update of Cannabis" with a "Pre-review of Cannabis". In this way, the ECDD could decide to conduct a Critical Review in its next meeting, which could then lead to scheduling recommendations to the Commission on Narcotic Drugs. Such a decision would not be possible when the agenda item is an Update.

A Pre-review requires that the ECDD considers the pertinent information on the subject. Therefore, for this purpose, DrugScience prepared this Pre-review Report of cannabis and cannabis resin (also including their preparations). This Pre-review Report has been prepared with the same rigour as if it would have been prepared by the WHO Secretariat. It meets the standards as outlined by the Executive Board in its *Guidance on the review of psychoactive substances for international control*. (World Health Organization, 2010)

The report has been written by an independent expert team with a broad knowledge and expertise, including the medical and non-medical use of cannabis, assessment of clinical evidence, pharmaceutical production methods of cannabis, and legal and administrative aspects of drug control. In this respect, their expertise is even broader than usual for ECDD review reports.

The scheduling under the Single Convention on Narcotic Drugs assumes a scientific justification. However, cannabis and cannabis resin have never been evaluated by WHO since it was mandated the review of psychoactive substances in 1948. The last evaluation for the international substance control conventions were therefore when the League of Nations evaluated them in 1924 and 1935.

The only recommendations by the Expert Committee were repeated recommendations in the 1950s and the 1960s calling on countries not to allow medical use of cannabis. These recommendations still stand. Not only are they at the basis of the prohibition of medical use in many countries but they are also the justification for inclusion of cannabis and cannabis resin in Schedule IV of the Convention, which classifies them among the substances with the strictest prohibition.

With this report, DrugScience enhances the ability of the World Health Organization and its Expert Committee on Drug Dependence in fulfilling its international obligations and

enables the Expert Committee to arrive at an independent and scientific recommendation whether a Critical Review is warranted or not.

Professor David Nutt, DM, FRCP, FRCPsych, FMedSci
Chair,
DrugScience

Abbreviations and acronyms

AUC	area under the curve
CBD	cannabidiol
CBN	cannabinol
CB_1R	Cannabinoid type-1 receptor or CB_1 receptor
CND	Commission on Narcotic Drugs
CFU	colony forming units
CSF	cerebral spinal fluid
DSM	Diagnostic and Statistical Manual
eCB	endocannabinoid
ECDD	Expert Committee on drug Dependence
EMCDDA	European Monitoring Centre on Drugs and Drug Addiction
GAP	Good Agricultural Practices
GDP	Good Distribution Practices
GLcP	Good Laboratory control Practices
GMP	Good Manufacturing Practices
IACM	International Association for Cannabinoid Medicines
INCB	International Narcotics Control Board
IQ	intelligence quotient
ISCD	Independent Scientific Committee on Drugs
MS	multiple sclerosis
NNT	number needed-to-treat
MW	molecular weight
PET	positron emission tomography
RA	rheumatoid arthritis
RCT	randomised controlled trial
THC	tetrahydrocannabinol
UHR	ultra-high risk
UNODC	United nations Office on Drugs and Crime
WHO	World Health Organization

Introduction

A Pre-review for the scheduling of Cannabis and Cannabis resin under the international drug control conventions is much needed, as explained in the Foreword by Professor David Nutt. This Pre-review Report provides the data for such a Pre-review by the WHO Expert Committee on Drug Dependence.

The purpose of a Pre-review is to determine whether current information justifies a Critical Review. For evaluating substances in a Pre-review, the categories of information are identical to those used in Critical Reviews. At the stage of the Pre-review, the Expert Committee must decide whether the information justifies a Critical Review. If it finds that the data available may justify changing the scheduling of cannabis and/or cannabis resin, the Committee should recommend a Critical Review in its next Meeting. The Pre-review is a preliminary analysis, and findings at this stage should not determine whether the control status of a substance should be changed.

If the Committee decides that a Critical Review is warranted, there will be a number of assessments to be made by the Committee in its next session:

The current control is through Schedules I and IV of the Single Convention on Narcotic Drugs as amended by the 1972 Protocol. When reviewing it, cannabis needs to be assessed against the criteria for listing a substance in these two Schedules in order to determine whether they are still met today. If not, the question is whether cannabis meets the criteria for other Schedules, particularly Schedule II of the Single Convention, or does not meet the criteria for any scheduling.

The full procedure to arrive at a decision is presented in the *Guidance on the WHO review of psychoactive substances for international control.* (World Health Organization, 2010) However in short, the pertinent criteria for the Critical Review of cannabis and cannabis resin are the following:

1. The applicability of the Single Convention should be assessed, before considering the Psychotropic Substances Convention; if a substance is cannabis-like and the Committee decides that it should be scheduled, it should be scheduled under the Single Convention.
2. The next step is to decide whether a substance is "liable to similar abuse and productive of similar ill-effects as the substances already in Schedule I or II". If this is the case, the Committee should recommend scheduling, if not, it should recommend removal from all Schedules.

For substances already scheduled under the Single Convention, Article 3, paragraph 6 applies and not Article 3, paragraph 3. This makes a difference in so far that substances already scheduled can be moved to another schedule or completely removed. Because paragraph 3 of the same article is not applicable to substances already scheduled, its "similarity-rule" (that requires that the ECDD assesses whether the substance under review is cannabis-like) does not apply either. This is supported by the official Commentary to the

Convention concerning the scheduling of cannabis and its resin in Schedule IV: "…Should the results of the intensive research which is at the time of this writing being undertaken on the effect of these two drugs so warrant, they could be deleted from Schedule IV, and these two drugs [i.e. cannabis and cannabis resin], as well extracts and tinctures of cannabis, could be transferred from Schedule I to Schedule II." (Anonymous, 1973a) The quote shows that there is also no impediment for the Committee to recommend a deletion if it should conclude that this is justified.

3. In the next step, the Committee should decide whether Scheduling should be in Schedule I or II. Unfortunately, neither the text of the Convention nor the Guidance provide criteria for the choice for Schedule I or Schedule II. However, the official commentary to the Single Convention explains that the criteria used by the Technical Committee of the Plenipotentiary Conference (i.e. the Conference of the countries that negotiated the conventions in the 1950s and 1960s) included that dependence-producing properties stronger than codeine and more or less comparable to morphine led to Schedule I and dependence-producing properties not greater than those of codeine but at least as great as those of dextropropoxyphene led to listing in Schedule II. Although this seems to be clear, the full list of criteria used by the Technical Committee is confusing and intrinsically contradictory, including a criterion on comparability to cannabis and cannabis resin. (Anonymous, 1973)

4. If the Committee recommends the substance to be scheduled in Schedule I, it should also assess whether it 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." (Anonymous, 2009)

Moreover, there exist recommendations by the Committee from 1955, 1960, 1965 and 1968 that cannabis and cannabis resin should not be used medically. Because these recommendations were never revoked, they still stand. However, since then much progress has been made in research, and also the professional cultivation of herbal medicines has been standardized in several cases, resulting in reproducible products. Moreover, a cannabis extract with the status of a licensed medicine is available in 28 countries. This requires that the Committee provides clarity by either repeating or revoking the earlier recommendations on this issue.

Finally, an increasing number of countries adopt alternative policies to mitigate the harm of cannabis and its prohibition. In many countries legal provisions exist that allow people in one way or another to produce and use cannabis without fear of legal prosecution. These provisions have many names: legalization, regulation, condoning etcetera. As a consequence, many people are exposed to cannabis more or less legally, but the quality is not always ensured. This exposes users unnecessarily to hazards from impurities that should and could be avoided, such as moulds and fungi (esp. *A.* fumigatus), heavy metals and pesticides.

The Committee, being a panel with specific pharmaceutical expertise, should make recommendations to those jurisdictions allowing the production and use of cannabis to establish quality assurance systems. As the latter two issues are somewhat separate from the

recommendations on scheduling, the Committee can, if it prefers to do so, make recommendations on medical use and quality control already during its current session.

1. Substance identification

A. International Nonproprietary Name (INN) and other generic designations

There is no INN for Cannabis sativa L.

The main active constituent of cannabis is *dronabinol INN*. Dronabinol is often also called Δ^9-tetrahydrocannabinol, or tetrahydrocannabinol (THC), ***In this document, dronabinol, Δ^9-tetrahydrocannabinol, tetrahydrocannabinol and THC are used as synonyms.***

Cannabinol (another natural cannabinoid) has been assigned an INN as well.

No other constituents are assigned an INN.

Moreover, a standardized cannabis extract containing Δ^9-THC and cannabidiol has been denominated *nabiximols USAN*. The USAN system is coordinated with the INN system and therefore a future identical INN designation for this extract may be possible.

B. Botanical classification

Order: Rosales
Family: Cannabaceae
Genus: Cannabis L.
Species *Cannabis* sativa L.

C. Chemical Abstract Service (CAS) Registry Number

Not applicable

D. Proprietary names

Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Bedropuur® and Bedrolite®
are varieties of commercially available pharmaceutical grade herbal cannabis
Sativex® is a standardized extract of cannabis (nabiximols USAN)
(Marinol® is dronabinol INN)

E. Colloquial names

There are more than 100 street names in English and dozens in virtually every other major language. In English they include cannabis, marijuana, skunk, herb, resin, weed, ganja, purple haze, northern lights, charis, Thai sticks, grass, pot.

F. WHO Review history[1]

Cannabis and Cannabis Resin are scheduled in Schedules I and IV of the Single Convention on Narcotic Drugs since the Convention has been agreed. (Anonymous, s.a.)

[1] This section is based on a document prepared by the author for the 36th Meeting of the Expert Committee on Drug Dependence.

These substances were discussed internationally for the first time at the The Hague Conference of 1912, (International Narcotics Control Board, 1978) but it was only the second Opium Convention of 1925 that regulated the international trade of "Indian hemp", its resin and its galenic preparations. It allowed for the medical and scientific use of galenic preparations. (International Narcotics Control Board, 1978; Danenberg et al., 2013)

Cannabis was reviewed by the Health Committee of the League of Nations in 1935, which recommended that preparations obtained from cannabis extract or tincture were placed under control of the second Opium Convention. (International Narcotics Control Board, 1978; Danenberg et al., 2013)

After World War II, WHO became responsible for the health functions of the League of Nations. The Expert Committee on Drugs Liable to Produce Addiction, later called the Expert Committee on Addiction-Producing Drugs (and today called the ECDD) spoke out against the medical use of cannabis repeatedly (e.g. fifth (1955), 11th (1960), 14th (1965) and 16th Sessions (1968)). (World Health Organization, 1955; World Health Organization, 1960; World Health Organization, 1965; World Health Organization, 1968) However, in none of these cases there was a review of the dependence-producing properties of the substance. A document by the International Narcotics Control Board (INCB) mentions that WHO produced a report on the physical and mental effects of cannabis in 1953, but this document was lost over time. It is not clear whether the Expert Committee on Drugs Liable to Produce Addiction was involved with it. (International Narcotics Control Board, 1978; Wolff PO, 1955)

Because of their inclusion in the 1925 Opium Convention, cannabis and cannabis resin were later included in Schedule I of the Single Convention on Narcotic Drugs, when this convention replaced an earlier drug control convention in 1961. When the Schedules of the Single Convention were drawn up, the Expert Committee on Addiction-Producing Drugs stated that it "believed that the composition of the schedules (on the draft list for the Single Convention) should be most carefully reviewed before they become an established part of the new Convention". (World Health Organization, 1959) Yet, the Expert Committee's tenth report only mentions that substances in Schedule III were reviewed individually, whilst the review of other Schedules seem to have been a quick check of the lists with a few remarks to move substances to other Schedules. No reference is made to a review of cannabis and/or its resin. (Danenberg E et al., 2013; World Health Organization, 1960) The Expert Committee's 13th report also mentions a review of substances for the Single Convention without a specific reference to a review of cannabis or cannabis resin. (World Health Organization, 1964)

The Technical Committee of the Plenipotentiary Conference, which was the conference of the countries where the Single Convention was negotiated, included both substances also in Schedule IV. The Technical Committee used the following criteria for inclusion: Substances "(a) Having strong addiction-producing properties or a liability to abuse not offset by therapeutic advantages which cannot be afforded by some other drug; and/or (b) For which the deletion from general medical practice is desirable because of the risk to public health". (Anonymous, 1973c)

Of interest is also that the 35th Expert Committee on Drug Dependence conducted a Critical Review of dronabinol in 2006 and recommended to move the substance from Schedule II of the United Nation Convention on Psychoactive Substances to Schedule III. (World Health Organization, 2006a; World Health Organization, 2006b) This was rejected then by the Commission on Narcotic Drugs without making mention of what the required social or economic considerations for such a rejection were. (Commission on Narcotic Drugs, 2007) Although dronabinol is regulated as a separate identity under the drug control conventions, this is important because it is also the main constituent of cannabis and cannabis resin.

In 2009, the Commission on Narcotics Drugs (CND) requested in its Resolution 52/5 "Exploration of all aspects related to the use of cannabis seeds for illicit purposes", "the United Nations Office on Drugs and Crime to share information regarding the health risks posed by cannabis with the Expert Committee on Drug Dependence of the World Health Organization, and, in that regard, looks forward to an updated report on cannabis by the Expert Committee, subject to the availability of extra budgetary resources". (Commission on Narcotic Drugs, 2009)

From 1968 until 2014, cannabis has never appeared on the agenda of the Expert Committee. From 2014 onward, the 35th, 36th and 37th Meetings of the Committee agreed to review cannabis in a future meeting of the Committee. (World Health Organization, 2012)

This has not been substantiated so far and only "intermediate" documents have been discussed. (Madras BK, 2015; Anonymous, 2014)

In 2016, WHO published the report "The health and social effects of nonmedical cannabis use". (World Health Organization, 2016) However, although useful, this report was not prepared for conducting a review by the Committee and does not cover all the required topics or meet the required format.

2. Botany and chemistry

A. Description of the plant

UNODC describes the physical appearance as 'Cannabis is an annual, dioecious, flowering herb. Staminate (male) plants are usually taller but less robust than pistillate (female) plants. Stems are erect and can vary from 0.2-6 m. However, most of the plants reach heights of 1-3 m. The extent of branching, like the plant height, depends on environmental and hereditary factors as well as the method of cultivation'. (United Nations Office on Drugs and Crime, 2009) An image of a male and a female plant are shown in Figure 1.

B. Plant varieties

Often two varieties are distinguished: *Cannabis* sativa L. spp. sativa and *Cannabis* sativa L. spp. indica. There are morphological and chemical differences between these two.

Within the subspecies, there are numerous varieties. Some distinguish a third subspecies: *Cannabis* sativa L. spp. ruderalis.

Figure 1. A flowering male and seed-bearing female plant. 1. male flower, enlarged detail; 2. and 3. pollen sac of same from various angles; 4. pollen grain of same; 5. female flower with cover petal; 6. female flower, cover petal removed; 7. female fruit cluster, longitudinal section; 8. fruit with cover petal; 9. same without cover petal; 10. same; 11. same in cross-section; 12. same in longitudinal section; 13. seed without hull. (Köhler FE. Köhler's Medizinal-Pflanzen in naturgetreuen Abbildungen und kurz erläuterndem Texte. 1887)

C. Treaty definitions

Cannabis is defined in the Single Convention on Narcotic Drugs as "the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated."

Cannabis resin is defined as "separated resin, whether crude or purified, obtained from the cannabis plant."

It should be noted that what the Conventions consider to be cannabis and cannabis resin does not refer to the whole plant. Thus, treaty definitions are narrower than the botanical definition. Other parts of the plant are not under international control.

D. Constituents[2]

Over 60 cannabinoids have been identified in *Cannabis* sativa L., but many of these are not or only marginally explored for their properties. (Pertwee RG, 2004) The two main

[2] This subsection is based on a document prepared by the author for the 36th Meeting of the Expert Committee on Drug Dependence.

cannabinoids in most varieties are Δ-9-tetrahydrocannabinol and cannabidiol (CBD). Other cannabinoids naturally occurring in the plant include cannabichromene, cannabigerol, cannabichromevarin, tetrahydrocannabivarin etcetera. All the cannabinoids are present as carboxylic acids and are decomposed on heating into the free cannabinoids. Cannabinol is present in dried cannabis, but is a decomposition product. All these cannabinoids differ in pharmacodynamical properties: agonists, partial agonists or antagonist, with different affinities to the various cannabinoid like receptors, such as CB_1, CB_2 and the Transient Receptor Potential V1 (TRPV1) or vanilloid receptor. The free cannabinoids have different activities than the cannabinoid acids. Some cannabinoids may be pharmacologically inactive.

Usually, varieties of *Cannabis* sativa L. spp. sativa are relatively strong on tetrahydrocannabinol, while varieties of *Cannabis* sativa L. spp. indica are relatively high on cannabidiol.

Moreover, plant material contains many substances from various other chemical classes, such as terpenes and flavonoids. The typical number of substances that can be identified in a plant is 700 – 1000, most of them not psychoactive. However, it should be considered that these other constituents may act as uptake enhancers (i.e. bioavailability enhancers) for other substances, e.g. this is known to be the case for some terpenes. (Kesarwani K and Gupta R, 2013)

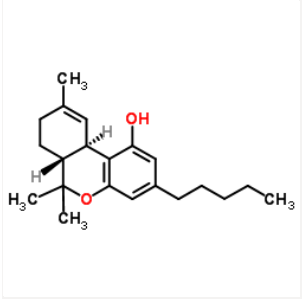
Both plant genotype and phenotype can make a difference for the actual composition of a cannabis batch. These differences can have consequences for the psychopharmacological and other pharmacological activity of the plant. (Scholten WK, 2006) Therefore, there is not "one cannabis": the actual content of tetrahydrocannabinol in the flowering tops can vary from very low (under 0.9 % for the approved industrial varieties in the EU, to up to 28 %). Moreover, the variety in cannabinoid profiles and the presence of different uptake enhancers cause a diversity of properties of the many cannabis varieties.

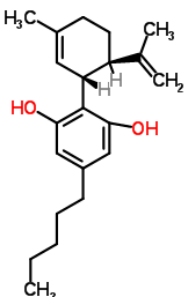
E. Chemical formulas of some main constituents

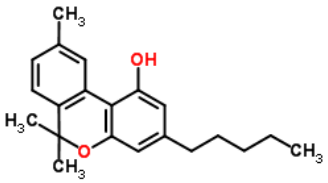
dronabinol: $C_{21}H_{30}O_2$
cannabidiol: $C_{21}H_{30}O_2$
cannabinol: $C_{21}H_{26}O_2$ (Chemspider, website)

F. Structural formulas of some main constituents

dronabinol: cannabidiol: cannabinol:







G. Molecular weights of some main constituents

Molecular weight (M.W.) of dronabinol:	314.46 gram/Mol
M.W. of cannabidiol:	314.46 gram/Mol
M.W. of cannabinol:	310.43 gram/Mol

H. Melting points of some main constituents

dronabinol:	200	°C
cannabidiol:	66	°C
cannabinol:	76.5	°C

I. Cultivation

The illicit cultivation of cannabis has been comprehensively described by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), which has been used to draft the subsections on outdoor and indoor cultivation. We refer for more details to its report on this topic.(European Monitoring Centre for Drugs and Drug Addiction, 2012a)

Open air cultivation

Originating from Central Asia, the cannabis plant had already spread around the world in ancient times. It served for the production of fibres (hemp for ropes and cloth), the extraction of oil from the seeds (for culinary purposes and as lamp oil) and for its psychoactive properties. Nowadays, there is open air cultivation almost around the world, as the plant will grow up to a latitude of 55°N.

For the cultivation of the fibres, both the male and female plants are cultivated. The plants are sowed in spring (late April or May) and the harvest takes place relatively early. The stems of the plants, usually 2 -3 meters high and even higher at times, are put in water in order to make them rot. After this "retting", the fibres can be set free by crushing the stems.

For the production of drug, the goal is to obtain the flowers. Because the plant starts flowering only when the days start shortening, the harvest is much later in the season than for fibre hemp, usually at the beginning of October. In countries closer to the equator however, varieties are adapted to the more constant day length and start flowering when sufficiently mature.

If the plant is cultivated by sowing, there will be male and female plants and the flowers will contain seeds at the moment of harvesting. Another option is to clone female plants selectively. This will result in seedless flowers ("sensimilla"), which have usually a higher content of tetrahydrocannabinol.

In southern and eastern Europe, in Asia and in Africa, the prevailing method of hemp cultivation is outdoor, while in most western and northern European countries there is a preference for indoor cultivation. In more northern countries, bad weather conditions can ruin the crop because the flowers will rot before they are fully grown.

To harvest the herbal cannabis (or "marijuana", as the product is called in the USA), the flowers and upper leaves are cut from the plant and allowed to dry, then compressed into dense blocks to minimize the volume for transportation.

Cannabis resin is prepared by trashing and sieving the sun-dried flowers. In this way the gland cells containing the essential oil with the cannabinoids are separated. They are compressed, resulting in a dark-brown resin. Because of differences in processing, resin originating from various countries can be very different.

Indoor cultivation

In case of illicit production, indoor production has the advantage that it can be hidden more easily, although premises with indoor production can be detected with Infra-Red (air) photography and by identifying buildings with high electricity consumption.

Through indoor cultivation, the environment can be better controlled, and hence, the product properties too, especially if not grown in glass-houses but in sealed rooms. Temperature, lighting (including day length), humidity, watering and fertilization can be controlled to a very high level. This is at a higher cost, mainly because of the electricity needed for the powerful lamps in use (typically 400 – 600 W/m^2); however, the electricity is often stolen so the costs are not a concern for the illicit grower. By indoor cultivation it is possible to reach six to eight harvests per year.

Usually plants are grown in individual pots with soil, sometimes hydroponically. Once the plants are ready for harvesting, they are cut and hung to dry. After about two weeks, the flowering tops are cut off the plant and the leaves and stems are cut out by hand with scissors ("manicured").

Sometimes the waste from the manicuring and the leaves is used to separate and collect the glandular hairs using ice water and sieves. This result in a product called "modern hashish", which has potentially a high content of THC.

The main determinant for the yield is the strain, followed by the amount of lighting.

Cultivation for pharmaceutical purposes

For the cultivation of cannabis for pharmaceutical purposes, the same techniques can be used as described above. Some production of medical cannabis is illegal, and in some states in the USA the production of medical cannabis is in the hands of individuals, cannabis clubs, or (semi-) professional organizations with no supervision on the quality by the health authorities. On the other hand, legal producers apply very professional techniques in order to arrive at a product that meets all pharmaceutical requirements. Therefore, we may assume that all sorts of cultivation exists, from bad to excellent.

In some countries, including Canada, the United Kingdom and the Netherlands, the marketed product meets pharmaceutical standards. In the United Kingdom, where the production is intended to produce a standardized extract (Sativex®), the cultivation is partially standardized and after extraction, the concentration of the cannabinoids is adjusted until to the required level. In the Netherlands, where the inflorescence is prescribed to the patient, the cultivation is standardized to a high level, in order to have batch-to-batch consistency . Various products are available, and therefore the variety needs specification.

3. Ease of convertibility into controlled substances

The criterion for ease of convertibility has been set by the World Health Assembly in its Resolution 7.7 of 1954. A substance will be considered by the World Health Organization as "convertible" where the ease of conversion and the yield obtained constitute a risk to public health, and that in cases where there is uncertainty as to whether a substance will fall under this definition, the substance will be considered as "convertible" rather than as "not convertible". The Guidance on the WHO review of psychoactive substances for international control defines *Ease of convertibility* in its paragraph 49 as "A substance is convertible if it is of such kind as to make it, by the ease of the process and by the yield, practicable and profitable for a clandestine manufacturer to transform the substance in question into controlled drugs". (World Health Organization, 1954)

Related controlled substances which are candidate for being converted from cannabis are dronabinol (controlled under Schedule II of the Convention on Psychotropic Substances) and six stereoisomers of this substance (the 7,8,9,10-; 8,9,10,10a-; 6a, 9,10,10a-; 6a,7,10,10a-6a,7,8,9-; and 6a,7,8,9,10,10a- configurations of tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol). The latter are controlled under Schedule I of the same convention.

Cannabidiol and cannabidiolic acid can be extracted from fibrous hemp or from low THC containing hemp seeds using solvents and is then purified to a crystalline substance. (Cannabidiol Solutions, website) Cannabidiol obtained by decarboxylation is cyclized in the presence of Lewis acids in a non-polar solvent to produce dronabinol.

The fact that dronabinol and the other scheduled stereoisomers are never encountered in drug markets show that conversion is not an issue. Instead, similar products such as "cannabis oil" with high dronabinol content but lower purity are made in much simpler ways directly from cannabis or cannabis resin.

4. General pharmacology, including pharmacokinetics and pharmacodynamics

Pharmacodynamics

Most of the actions of cannabinoids are mediated by actions at two G-protein coupled receptors, named CB_1 and CB_2 receptors. In addition, there is evidence for non-receptor

dependent mechanisms of cannabinoids. The effects of cannabinoids can be blocked by selective receptor antagonists such as rimonabant. (Nutt DJ, 2005)

The CB_1 cannabinoid receptors are distributed in the central nervous system where they are the most dense of all G-protein coupled receptors (their total number exceeding that of dopamine, noradrenaline and serotonin receptors put together). CB_2 receptors are found in many peripheral tissues (spleen, leukocytes; reproductive, urinary and gastrointestinal tracts; endocrine glands, arteries and heart, etc.).

The brain makes several substances (called endogenous cannabinoids or endocannabinoids) such as anandamide and diacylglycerol that are agonists at cannabinoid receptors where they produce alterations in synaptic connectivity. The endocannabinoids are produced by breakdown of phospholipids in cell membranes during and after neuronal activity. Cannabis mimics the effects of the endogenous neurotransmitters anandamide and diacylglycerol. (Devane WA et al., 1992; Di Marzo V et al., 2001; Mechoulam R, Fride E and Di Marzo V, 1998; Segiura T et al., 1997)

Cannabinoids of herbal origin, particularly THC, mimic to a greater or lesser extent the effects of these endocannabinoids. (Grotenhermen, 2004) Not all naturally occurring cannabinoids exhibit the same pharmacological activity. They can have higher affinity to the CB_1, to the CB_2 or to the vanilloid receptor ($TRPV_1$), and they can be agonists, antagonists or partial agonist. (Pertwee RG, 2004)

Cannabis may inhibit endorphins in the emetic centre, suppress prostaglandin synthesis, and/or inhibit medullary activity through an unspecified cortical action. (Drug Bank, website)

CB-receptors are over 600 million years old. They are present all over the animal kingdom, even in the very primitive *Hydra* vulgaris (Pallas). CB receptors are much older than the cannabis plant, which dates back to the Oligocene (34 million years ago).[1] (McPartland JM and Guy GW, 2004) This is an indication that the endocannabinoid system has its own physiological function and that its origins are not related with the use of the cannabis plant. This physiological function exists inter alia in the modulation of pain experience and appetite.

The brain effects of THC are mediated via agonist activity at CB_1 receptors, which are found at high concentrations in brain areas associated with motivation and reward. THC has been shown to increase the release of dopamine from the nucleus accumbens and prefrontal cortex in rodents, an effect found with many substances of misuse. (Tanda G, Pontieri FE and Di Chiara G, 1997) However the human data are unconvincing. (Nutt et al., 2015)

THC is the main cause of the pharmacological effects of cannabis, including the medicinal benefits of the plant. It is an agonist to both the CB_1 and the CB_2 subtype of these receptors. It is thought that the anti-emetic effects are also partly mediated by the CB_1

receptor. THC also acts on CB_2 receptors and this action on those found in the immune system may explain its actions in inflammatory conditions.

Cannabidiol, which has two isomers, is another cannabinoid that has actions that in some ways oppose those of THC through as yet-to-be-understood mechanisms. The relative lack of cannabidiol in some forms of plant cannabis (e.g. skunk) may help explain different effects of these compared with the more balanced mixtures of THC and cannabis found in more traditional varieties. (See also Section 7. Dependence potential, Subsection "Cannabis and psychosis")

Cannabinol is not naturally occurring in the living cannabis plant, but it occurs usually in the dried herb as a degradation product of THC. Δ8-THC is another cannabinoid, which is present in the plant in small amounts.

Table 1. Effects of cannabinoids on various receptors. (Pertwee RG, 2004)

effect on:	CB_1-receptor	CB_2-receptor	$TRPV_1$
THC	++	+	0
Δ^8-THC	+	+	0
(+)-cannabidiol	+/-	+	+
(-)-cannabidiol	0	0	+
cannabinol	+/-	+	0

+ = agonist; +/- = partial antagonist; 0 = no effect

Pharmacokinetics of inhaled cannabis

Measuring the kinetics of cannabis reliably is not easy when it comes to smoking of cannabis cigarettes. Combustion takes place at 700 – 850° C and around 30 % of the cannabinoids is destroyed by pyrolysis during smoking. Bioavailability of smoking is reported as ranging from 2 – 56 %. (Grotenhermen F, 2003) By using a vaporizer device, the intake is more reliable and contrary to smoking, vaporizing is not associated with the inhalation of harmful combustion products such as polynuclear aromatic hydrocarbons and carbon monoxide (aside from nicotine and nitrosamines when cannabis is smoked as a mixture with tobacco).

Heat treatment during or before delivery of cannabinoids is necessary to generate CB receptor activity, as the cannabinoids occur in the plant as carboxylic acids. They are converted into free cannabinoids by decarboxylation at 180 – 200° C. This occurs both on smoking and vaporizing.

Eisenberg et al. studied the kinetics of dronabinol in predominantly male neuropathic pain patients aged 25 to 69 years (mean age ± SD: 42 ± 14). They used a metered dose inhalator (Syqe ®) that vaporized the cannabinoids at 190° C in 497 ms using pharmaceutical grade cannabis containing 19.9 % dronabinol, 0.1 % cannabidiol and 0.2 % cannabinol. Each

dose contained 15.1 ± 0.1 mg doses of processed cannabis flos, containing 3.08 ± 0.02 mg dronabinol. The efficiency of the THC vaporization process was 52.7 ± 2.7 %.

They found a mean plasma C_{max} for dronabinol for the entire group of 38 ± 10 ng/mL and T_{max} occurred after 3 ± 1 minutes. Mean dronabinol $AUC_{0\rightarrow infinity}$ was 607 ± 200 ng·min/ml. No measurable plasma levels of the active metabolite (11-OH-THC) were monitored within the time frame of the blood sampling (0–120 minutes). (Figure 2) (Eisenberg E, Ogintz M, and Almog S, 2014)

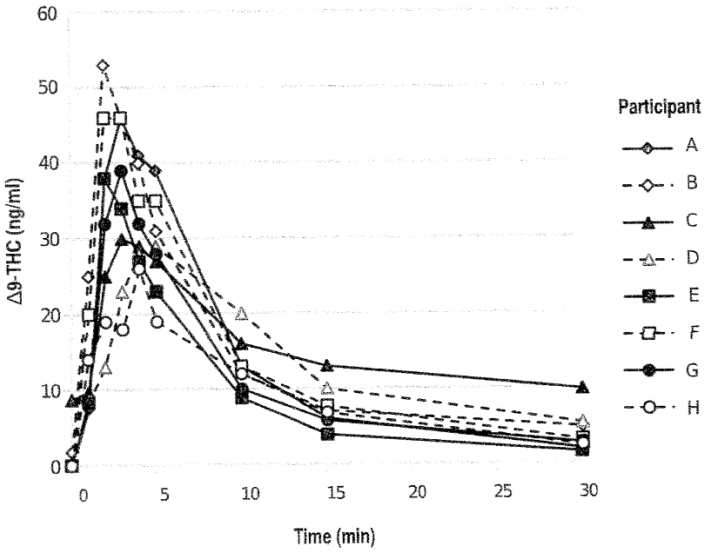


Figure 2. Δ9-THC plasma levels following single dose inhalation of 15.1 ± 0.1 mg processed cannabis flos, containing 3.08 ± 0.02 mg THC, by using Syqe Inhaler. (Eisenberg E, Ogintz M, and Almog S, 2014; reprinted by permission of the publisher)

Another study in 18 healthy volunteers compared dronabinol delivery using an electric vaporizer (Volcano®) compared with smoked cannabis. For both the vaporizer and the smoking the study applied the same standardized puff procedure. Subjects were instructed to continue puffing until they exhausted smoke or vapour from the delivery device or until they had inhaled as much as they could tolerate. Three strengths of cannabis (provided by the US National Institute on Drug Abuse) were used both for smoking and vaporizing. The authors found that inhalation by vaporizing and by smoking results in equivalent 6-hour AUCs and peak plasma-THC concentrations measured at 2 minutes. However, the authors also report that the vaporizer was associated with higher plasma-THC concentrations at 30 min and 1 h compared to smoking, suggesting that absorption was faster with the vaporizer. Of interest was that the systemic dose of THC, as estimated by the plasma AUC, normalized for the THC content of the cannabis, varied with THC strength. The AUC becomes relatively lower when the strength of the cannabis increases. (Abrams DI et al., 2007)

Pharmacokinetics of oral dronabinol (Marinol®)

(US Food and Drug Administration, 2004)

Absorption

Dronabinol (administered as Marinol®) is almost completely absorbed (up to 95 %) after a single oral dose. It undergoes first pass hepatic metabolism which with high lipid solubility leads to only 10-20 % of the dose reaching systemic circulation.

Distribution

Dronabinol has a large apparent volume of distribution due to its lipid solubility. It also has high plasma protein binding.

Elimination

The elimination phase is a two compartment model with an initial half-life of 4 hours and a second half-life of 25-36 hours. It is excreted in both faeces and urine.

Pharmacokinetic interactions

None identified but there is the possibility of dronabinol displacing other highly protein bound medicines.

Pharmacokinetics of sublingual cannabis extract (Sativex®)

(SPC Anonymous, website)

Absorption

Following administration of the spray both THC and cannabidiol (CBD) are absorbed and appear in the plasma within 15 minutes.

Distribution

The components are quickly distributed and absorbed into body fat. Protein binding is high and THC undergoes first pass metabolism in the liver.

Elimination

The first order elimination half-life is approximately 2-5 hours for THC and 5-9 hours for CBD depending on dose. The process is thought to be biphasic.

Pharmacokinetic interactions

Care is advised for co-administration of sedative medicines as there may be an additive effect. Strong enzyme inducing medicines such as rifampicin, some antiepileptics and barbiturates are not recommend. Medicines affecting cytochrome P systems need to be used with caution.

Secondary pharmacology

Effects on cardiovascular system

Marinol®: Palpitations, tachycardia, vasodilation
Sativex®: Alterations in heart rate and blood pressure

Effects on respiratory system

None described

Other pharmacological effects

Marinol®: Anxiety, confusion, dizziness, euphoria, hallucinations, paranoid reaction, somnolence. Nausea & vomiting.

Sativex®: Anxiety, illusions, changes in mood, paranoia, confusion, hallucinations and delusional beliefs

Routes of administration

Non-medical use

Non-medical use of cannabis and cannabis resin is usually by smoking as a cigarette, pure, or mixed with tobacco. Oral forms such a mixed in baking products ("space cake"), in butter or chocolate occur.

Medical use

Herbal cannabis: Usually not regulated and can be in various forms. In addition to the routes of administration for non-medical use, also use as a herbal tea (with or without butter to enhance the bioavailability of the lipophilic cannabinoids) and by inhalation after vaporization occur.

Hazenkamp et al. conducted a cross-sectional survey over the internet in five languages (German, English, Spanish, French, Dutch). 953 patients (614 male, 339 female) with a mean age of 40.7 years from 32 countries completed the questionnaire. Preferred modes of use were smoking of cannabis (62.9 %), inhalation of cannabis with a vaporizer (23.6 %), oral use of cannabis in baked goods (7.9 %), oral use of cannabis as a tea (2.4 %), and oral use of dronabinol/Marinol® (1.8 %). No significant differences in preferred modes of use were found in correlation to symptoms or diseases. (Hazekamp et al., 2011)

Marinol®: capsules of 2.5 mg, 5 mg or 10 mg dronabinol for oral administration.

Sativex®: oromucosal spray (each containing 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol in 100 microliters).

Dosages

Non-medical use

The average amount of cannabis in a joint ("spliff") equates to between 6 and 10 mg THC. People who have used a lot and so developed tolerance may use more.

Medical use

Herbal cannabis: Usually not regulated; medical patients will titrate their intake depending on the relief of their complaints. They do not usually strive for a high (in fact many stop using it if the get high as they do not like the effect).
Marinol®: 2.5 mg to 20 mg daily.
Sativex®: 1-12 spray doses per day (equivalent to 2.7 – 32.4 mg dronabinol and 2.5 – 30 mg cannabidiol).

5. Experimental toxicology

In recent years the toxicology of cannabis has been studied more systematically than in the past through the research on new pharmaceutical preparations. In the past, many studies claimed to have some outcome, but some of the studies did not even declare the THC-content of the cannabis which was used, making them less meaningful. With a number of companies doing research for having a product approved for medical purposes, "cleaner" research has become available. It is for this reason that this section draws with emphasis on studies which have been conducted for the market application of Sativex® , which is currently the single cannabis product having market authorization.

Animal studies

Cannabis is a remarkably safe substance in terms of its acute toxic effects. THC is the component of cannabis which has the highest direct toxicity in all animals so far tested. In addition to older studies of cannabis and THC the recent introduction in many countries of the pharmaceutical preparation Sativex® (a solution containing a balanced mixture of THC and cannabidiol, see Section 11) has provided considerably more safety data as per current medicine development guidelines (*these data are in italics in the following sub-sections).*

Single-dose toxicity

The cause of death in experimental animals is usually respiratory suppression (Rosencrantz, 1983). The LD_{50} on intravenous administration is 40 mg/kg in the rat, but phylogenetically higher animals are less susceptible so the LD_{50} is around 130 mg/kg in the dog and monkey (Rosencrantz H, 1983; Rosencrantz H, Fleischman RW and Grant RJ, 1981).

Repeated-dose toxicity

The SPC for Sativex® reports "Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use". (Anonymous, website)

Reproduction function

The SPC for Sativex® reports *"Reprotoxicity studies carried out with the THC and CBD extracts present in Sativex showed no adverse effects on either male or female fertility in terms of numbers of animals mating; number of fertile males and females, or on copulation or fertility indices. There were reduced absolute weights of epididymides, with a "no-effect" dosage level of 25 mg/kg/day (150 mg/m^2) for male fertility. Data from the literature have shown negative effects of THC and/or CBD on sperm number and motility."*

Embryo-foetal and perinatal toxicity

In studies in animals, as expected, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Following repeated dosing, cannabinoids are concentrated in breast milk (40 to 60 times the plasma level). Doses in excess of normal clinical doses may affect growth rates of breast-fed infants. (Astley SJ and Little RE, 1990)

More recent data in the The SPC for Sativex® reports "*The "no-effect" dosage levels for effects on early embryonic and fetal survival, in rat studies, were approximately 1 mg/kg/day (6 mg/m^2), which is close to or less than the likely maximum human dosage level of Sativex. There was no evidence to suggest any teratogenic activity in either rats or rabbits at dosage levels considerably in excess of likely human maximum dosage levels. However, in a rat pre- and post-natal study, pup survival and nursing behaviour were impaired at doses of 2 and 4 mg/kg/day (12 and 24 mg/m^2] respectively.* It should be noted that though this may be due to a change of taste in the milk rather than an effect of cannabis on the neonate. (Chao FC et al., 1976)

Mutagenic and carcinogenic potential

This area has been subject to significant research interest in an attempt to discover evidence that smoking cannabis could be carcinogenic. The available evidence suggests that cannabis smoked alone (that is without tobacco) has a low potential of lung cancer, but when used mixed with tobacco the risks from tobacco become apparent. However, because it burns at a lower temperature than tobacco leaf, cannabis may reduce the toxicity of tobacco (UK Home Office unpublished research). The evidence from Sativex® licensing data and post-marketing surveillance shows this formulation meets current pharmaceutical safety criteria of low/zero carcinogenic risk and there is no reason to suppose other non-smoked forms of cannabis will behave differently. It is important to note that there are a number of anecdotal reports that cannabis may have anticancer activity. One clinical trial showed THC efficacy in a gliomas (a form of brain tumour).(Arney K, 2012; Guzmán M et al., 2006.)

Immunotoxicity

This has been a highly controversial area in years gone by in an attempt to justify the continued ban of cannabis or to justify its medical use. More recently a role has been postulated because of the presence of CB_2 receptors on immune cells. However no clear evidence of impact in either direction has been forthcoming and the growing Sativex® data

shows no signal of concern re effects to alter in any way immune function. Indeed, there is evidence that it can reduce damage in disorders where over-inflammation is a problem e.g. ulcerative colitis (http://www.gwpharm.com/inflammation.aspx)

Neurotoxicity

Cannabis does not appear to have any significant effects on brain morphology even when used for many years. In terms of brain activity and connectivity some studies have found increase while others found decrease. However, there is no clear meaning in terms of their explaining functional changes described in the sections below on cognitive and other brain functions. (Weiland BJ et al., 2015)

Human studies

For obvious ethical reasons there is no experimental evidence to determine a lethal dose in humans. Nor is there any clinical evidence, since there have been no proven cases of death directly attributable to cannabis poisoning. Extrapolating from the monkey data of 130 mg/kg mentioned above suggests that the lethal human dose of then the toxic dose of THC in a 70 kg adult would be around 9,1 gram THC. In a person of 70 kg, this relates to 32.5 grams of cannabis with a very high THC content (28 %), 60.5 gram of cannabis with an average THC content (15 %), or 114 gram of cannabis low on THC (8 %).

The usual dosing of cannabis delivers around 10 mg so this gives a safety ratio (lethal dose to recreational/therapeutic dose) of around 10,000 times in non-tolerant users. In comparison, the safety ratio for alcohol is about 10 times and heroin 5 times. Cannabis is therefore orders of magnitude safer on acute administration than most other psychoactive substances used non-medically.

Pregnancy

There is little if any evidence that cannabis use in pregnancy has significant effects on the fetus. If there was a meaningful effect the extensive increased in use of cannabis in the past 50 years would surely have revealed an association.

Lactation

Available pharmacodynamics / toxicological data in animals have shown excretion of THC and its metabolites in milk. (see Embryo-foetal and perinatal toxicity; above in this Section)

6. Clinical toxicology and adverse reactions in humans

Clinical experience

Adverse effects

Marinol®

Asthenia, palpitations, tachycardia, vasodilation, nausea, vomiting, anxiety, confusion, depersonalization, dizziness, euphoria, hallucination, paranoid reaction, somnolence, abnormal thoughts.

Sativex®

Dizziness and fatigue stated to be very common. Common effects include Asthenia, anorexia, constipation, diarrhoea, nausea, vomiting, anxiety, confusion, depression, dizziness, euphoria, hallucination, paranoid reaction, somnolence, abnormal thoughts, blurred vision, vertigo.

Non-medical experience

Smoking cannabis can lead to respiratory irritation and in rare cases with heavy use damage to the lung alveolae leading to cavitation. In Europe it is often smoked mixed with tobacco so the toxic effects of both are experienced.

Cannabis increases vascular engorgement in the conjunctiva (red eye).

Fatal intoxications

The few deaths in which cannabis has been implicated are mostly in middle-elderly men with pre-existent cardiovascular disease that is exacerbated by the cannabis-induced rise in blood pressure.

Non-fatal intoxications

The effect of cannabis in the brain is a feeling commonly described as being “stoned”. The ‘stoned’ experience varies considerably depending on the individual’s prior experience of cannabis the setting and the type of cannabis ingested (D’Souza et al., 2008; Morgan et al., 2010a). Common desired effects include heightened awareness of music, sounds, colours, textures and tastes disinhibition, giggliness and increased appetite. (Tyler A, 1986) Such alterations in perception and insight can impair judgement and coordination leading to an increased risk of accidents particularly if driving or operating complex machinery. Anxiety is common especially during the onset of drug effects. In people with pre-existing psychosis, cannabis can worsen symptoms such as paranoia and auditory hallucinations. Adolescents may be more vulnerable to cannabis-induced harms than adults. (Curran et al, 2016) In healthy controls cannabis intoxication has been used as an experimental medicine model for psychosis. (Curran & Morgan, 2014)

Cognition, learning and memory

Acute effects

Acute effects are transient and seen in the time period during which the individual is intoxicated with the drug (e.g. feeling 'stoned' for around 5-120 minutes when a spliff is smoked). A single dose of cannabis or THC robustly and dose-dependently impairs human working and episodic memory. (Curran et al. 2002; Crane et al., 2013) Memory impairments occur however the drug is administered, but the onset of effect is more rapid when it is inhaled or given intravenously than when it is ingested orally. Specifically, the encoding of new memories is impaired during cannabis intoxication and this leads to subsequent deficits in recalling these memories; by contrast, the retrieval of old memories that were consolidated when not under the influence is unaffected. Cannabis-induced working-memory deficits are seen more in the ability to manipulate information while it is 'online' (for example, when doing mental arithmetic) than in the ability to simply retain it for brief periods (for example, when remembering a new password code number before entering). Brain imaging studies show THC prevents the increased activity with increased working memory load in corresponding brain areas. (Bossong et al., 2012)

These effects on memory are consistent with the extensive *preclinical evidence* of: the amnestic effects of cannabis in animal models; the high density of cannabinoid receptors in memory-associated brain regions such as the hippocampus, amygdala and prefrontal cortex and observations that THC induces disruption of plasticity in the hippocampus.

Some studies report acute THC-induced impairment of behavioural inhibition and increases in impulsivity, but findings on attention, decision-making and risk-taking tasks are mixed and task-dependent. (Crane NA et al., 2013; Crean RD, Crane NA and Mason BJ, 2011). There is also some evidence that acute effects may vary depending on an individual's previous level of use of the substance. Tolerance to the memory-impairing and psychomotor effects of acute THC has been shown in individuals who use the cannabis more than once a week, probably reflecting a downregulation of cortical CB_1Rs. (D'Souza DC et al., 2008; Ramaekers JG et al., 2011)

There is some evidence that the acute memory-impairing effects of THC can be lessened when individuals smoke cannabis containing high levels of CBD. (Morgan CJ et al., 2010; Englund A et al., 2013) One study showed CBD alone enhanced fear extinction learning in humans. (Das RK et al., 2013) A recent cross-sectional study found that CBD appeared to protect against the effects of THC on hippocampal volume loss. (Yucel et al., 2016).

Long-term effects

Although in several countries legislation will enable new studies of medical cannabis to use prospective, randomized controlled trial designs, to date studies of the neurocognitive effects of long-term use of cannabis have relied mainly on retrospective, self-reported drug use by people who use cannabis non-medically. More objective indices of drug use can be

obtained through hair samples, although these are also somewhat limited (e.g. influenced by hair dyes) and have been rarely used in studies. (Han E, Chung H and Song JM, 2012) Long-term impairments in memory have been reported mainly in frequent, heavy users, but confounding factors make it difficult to establish any cause-effect relationships between cannabis use and neurocognitive function. Such factors include baseline cognitive function prior to drug use; use of other cognitively impairing drugs like alcohol; types of cannabis used; age at which use started; and mental health problems, including depression and cannabis dependence.

The most consistently reported long-term effects are impairments of encoding new episodic memories, with some studies finding persistent deficits in the first few days of abstinence. There is increasing agreement that these deficits are no longer seen when the individual stops using cannabis for 28 days. (Crane NA et al., 2013) Functional neuroimaging studies have been mainly cross-sectional and very heterogeneous and it is not possible to infer any causative relation between long-term cannabis use and brain changes (cf. systematic review by Batalla et al., 2013)

Age-dependent effects: adolescence and adulthood

The endocannabinoid (eCB) system has a major role in neurodevelopmental and maturational processes (including synaptic pruning and white-matter development), and these processes are especially prevalent during adolescence. As cannabis affects the functioning of the eCB system, the human brain may be more vulnerable to psychoactive substances at the time when use of cannabis often begins.

Preclinical studies have shown that a single dose of THC results in greater impairments to spatial and non-spatial learning in adolescent rats than in adult rats. (Cha et al., 2006) Similarly repeated THC has a more negative impact on adolescents, producing persisting impairments in memory that are not seen with the same treatment in adult rats. (Schneider M and Koch M, 2007) When THC was repeatedly administered over 6 months to adolescent monkeys in doses that corresponded well to human self-administration (approximately 1–2 joints, 5 days per week), the usual pattern of accuracy improvements on a test of spatial working memory was blunted. (Verrico CD et al., 2014) Thus, the persistent effects of THC on cognition in animals are more evident when exposure coincides with the developing adolescent brain.

From studies with humans there is some evidence that neurocognitive function and aspects of brain architecture are more disrupted by cannabis when individuals start using it during adolescence, although there is little longitudinal research and a scarcity of direct comparisons with adult users (Curran HV et al., 2016). It is generally difficult to say whether differences between cannabis users and non-users in cognitive function and/or brain structure/function are consequences of cannabis use rather than existing prior to use. (Jager G et al., 2010; Curran HV et al., 2016) In terms of neurocognitive function, individuals who started using cannabis during adolescence have been reported to have greater deficits in visuospatial attention, verbal fluency and inhibition than do those who start in adulthood.

(Ehrenreich H et al., 1999; Gruber SA et al., 2012) A recent study directly compared the acute effects of cannabis in adolescents (16-17 year old males) and in adults (24-28 year old males). (Mokrysz C et al., in press). This is the first study of its kind and used a placebo-controlled, double-blind cross-over design. On active cannabis, working and episodic memory impairment was greater in adults than adolescents. By contrast, cannabis impaired response inhibition accuracy in adolescents but not in adults. These contrasting profiles of adolescent resilience and vulnerability show some degree of translation from preclinical findings, and may contribute to escalated cannabis use by human adolescents.

Effects persisting after stopping use.

Several studies of long-term effects after an individual stops using cannabis are converging to show that cognitive impairments do not persist beyond 4–6 weeks after abstinence (Pope HG et al., 2001; Schreiner AM and Dunn ME, 2012). Similarly, using positron emission tomography (PET) imaging, one study demonstrated that chronic cannabis users showed a downregulation of cortical CB_1Rs that correlated with years of use. (Hirvonen J et al., 2012) After ~4 weeks of continuously monitored abstinence from cannabis at a secure research unit, their CB_1R density returned to control levels, further supporting recovery within 4 weeks, and even, according one recent study, after as little as 2 days (D'Souza DC et al., 2015)

Cannabis, IQ and educational achievement

To date, there have been three large prospective cohort studies that have assessed the relationship between cannabis use and IQ. In a New Zealand birth cohort study of 1,037 38-year olds born in 1972 or 1973, persistent cannabis dependence was associated with a decline of up to 6 IQ points from that measured at age 7-13 years (Meier et al., 2012). The decline was particularly evident for those who developed cannabis dependence in adolescence, and remained apparent even for those who, at age 38 years, used cannabis less than once a week.

In contrast, a UK birth cohort study of 2,235 15–16-year-old adolescents born in 1991 or 1992 found that cumulative cannabis use was not associated with a lower IQ compared with non-using controls, once IQ measured pre-teen and various potential confounders (in particular, the adolescents' use of cigarettes and alcohol) were accounted for (Mokrysz C et al., 2016). Cannabis use was relatively low in this study, with only 72 adolescents reporting more than 50 lifetime cannabis exposures.

A US prospective cohort study of 3,066 17–20-year-olds found no difference in IQ change from that measured at age 9-12 years between monozygotic and dizygotic twins discordant for cannabis use.[164] However, there were only 47 discordant twin pairs in which the cannabis-using twin had used cannabis frequently (more than 30 cumulative uses, and/or daily use), limiting the strength of any conclusions from this study.

The UK and US studies therefore both suggest that genetic or environmental factors drive the observed associations between lower IQ and cannabis use, although both cohorts included younger participants with fewer cannabis exposures than did the New Zealand study.

To date, all studies have relied on retrospective self-report of cannabis use, have ignored possible residual effects of the drug on IQ-test performance and have not addressed the potency or variety of cannabis used.

Several case-control and longitudinal studies have provided fairly consistent evidence of associations between adolescent cannabis use and both early school leaving and poorer educational performance. (Fergusson DM, Horwood LJ and Beautrais AL, 2003; Silins E et al., 2014; Lynskey MT & Hall W, 2000; Townsend L, Flisher AJ and King G, 2007) But the mechanisms producing these relationships remain hotly debated. (Verweij KJ et al, 2013) Some argue that heavy cannabis use results in cognitive and/or motivational deficits, which in turn result in poorer educational attainment. Others claim reverse causality - that poorer educational attainment leads to cannabis use (Fergusson DM, Horwood LJ and Beautrais AL, 2003; Lynskey MT and Hall W, 2000).

An alternative is that educational attainment and cannabis use may not be causally related but instead share common risk factors. (Fergusson DM, Horwood LJ and Beautrais AL, 2003; Silins E et al., 2014; Lynskey MT and Hall W, 2000; Townsend L, Flisher AJ and King G, 2007) This is supported by recent analyses showed that adjusting for teenage use of other substances attenuated the association between cannabis use and school attainment (Mokrysz C et al., 2016.; Hooper SR, Woolley D and De Bellis MD, 2014; Stiby AI et al., 2015). It is also supported by recent genetic studies that found no difference in early school leaving or years of education between both monozygotic and dizygotic twin pairs who were discordant for cannabis use. (Verweij KJ et al., 2013; Grant et al., 2012)

7. Dependence potential

Introduction

The dependence producing potential of cannabis is harder to assess than that of other substances. The UN scheduling is particularly relevant for drugs of the opioid class where clear scaling of reinforcing potential and self-use in animal models and humans is possible. This scaling has led to the defining by the Technical Committee of the Plenipotentiary Committee that negotiated the Single Convention, of the threshold for Schedule 1 as having a dependence like codeine or above and Schedule 2 as between codeine and dextropropoxyphene. As cannabis does not substitute for these opioids then a simple cross-reference of dependence potential is not possible. However as stated in Section 13, the percentage of users who become dependent on cannabis is significantly less than that for alcohol, cocaine, tobacco or Schedule 1 opioids. (Anthony JC, Warner LA and Kessler RC, 1994; Lopez-Quintero C et al., 2011).

Reinforcing effects

The reinforcing effects of cannabinoids in animals depend on species, route of administration and experimental design. Rats will perform a behavior such as level pressing to receive THC or CB_1R agonist infusions directly into the brain. (Braida D, Iosue S, Pegorini S and Sala M, 2004; Zangen A et al., 2006) However, it is difficult to get rats to perform for

intravenous THC self‑administration although this does occur in squirrel monkeys. (Justinova Z et al, 2005; Fattore L et al., 2001). The rewarding effects of THC in rats are dose-dependent and follow an inverted U-curve whereby large doses are less rewarding than medium doses; this has been shown in various experimental paradigms (e.g. conditioned place preference, intracranial self-stimulation. (Braida D, Iosue S, Pegorini S and Sala M, 2004; Gardner EL et al., 1988; Sanudo-Pena MC et al., 1997; Cheer JF, Kendall DA and Marsden CA, 2000) CBD does not influence the acute reinforcing effects of cannabis or the rewarding feeling of being 'stoned'. (Morgan CJ et al., 2010; Haney M et al., 2015)

In humans, THC produces the same inverted U-curve in terms of rewarding effects. THC produces the effects that users seek and so is the key reason for using cannabis. Human PET studies indicate that THC can increase dopamine release in the striatum although to a far lesser extent than do other recreational drugs, and not in all studies. (Bossong MG et al., 2015 Nutt DJ et al., 2015) THC-induced increases in opioid peptide release may also contribute to the rewarding effects of cannabis. (Manzanares et al., 1998; Valverde O et al., 2001)

Tolerance

Tolerance to cannabis and to THC occurs in both animal models and humans. Rats chronically exposed to THC show reduced CB_1R function throughout the brain which persists for days after THC treatment and then recovers; behavioural tolerance is also evident. (González S, Cebeira M and Fernández-Ruiz J, 2005; Hoffman AF, Oz M, Caulder T and Lupica CR, 2003) Similarly, humans who use cannabis chronically have been repeatedly shown to have CB_1R downregulation. (Hirvonen J et al., 2012; D'Souza DC et al., 2015)

Importantly, as with rodents, this effect reverses within weeks of humans stopping cannabis use (Hirvonen J et al., 2012) . Behavioural tolerance is also evident in humans and there is evidence of tolerance to the adverse cognitive effects of cannabis (D'Souza DC et al., 2008; Ramaekers JG et al., 2011)

Dependence and withdrawal

Although much research on cannabis and mental health has focused on psychosis, dependence is a far more common problem: we estimate that people who try cannabis are 9-fold more likely to become dependent on it than to develop psychosis in their lifetime (Moore TH et al., 2007; Kessler RC et al., 1994; Lopez-Quintero C et al., 2011).

The term 'dependence *syndrome* is defined by ICD-10 as being a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take the psychoactive substances (which may or not have been medically prescribed), alcohol, or tobacco. Symptoms use in ICD-10 diagnosis include tolerance, withdrawal, a strong desire or sense of compulsion to take the substance; difficulties in controlling substance-taking behaviour, progressive neglect of alternative pleasures, persisting with substance use despite clear

evidence of overtly harmful consequences In the *Diagnostic and Statistical Manual for Mental Disorders, fourth edition, text revision* (*DSM-IV-TR*), clinical problems associated with cannabis use were previously diagnosed as 'cannabis abuse' or 'cannabis dependence' In the most recent version (*DSM-5*) these categories were amalgamated into a single diagnosis of 'cannabis use disorder' (CUD).

A specific cannabis withdrawal syndrome is well recognized and affects around 50 % of daily users upon cessation of use, and typically begins 1–2 days after cessation, peaks at 2–6 days and remits at 1–2 weeks. (Budney AJ et al., 2004) Prominent symptoms include craving, sleep problems, nightmares, anger, irritability, dysphoria and nausea. (Allsop DJ et al., 2011) Cannabis withdrawal symptoms correlate with reductions in CB_1R availability during acute abstinence (D'Souza DC et al, 2015) and can be alleviated by THC in a dose-dependent manner. (Budney AJ et al., 2007) Cannabis is frequently rolled with tobacco in 'joints' and many users also smoke cigarettes. In daily users of cannabis and tobacco, individual withdrawal effects appear similar for both drugs; combined withdrawal produces stronger effects than does withdrawal for either one alone. (Budney AJ et al., 2004)

Vulnerability factors

Only a minority of cannabis users become dependent; therefore, what factors must predict vulnerability? Concurrent tobacco use has been identified as a risk factor, as have early adolescent onset and frequent (especially daily) use. (Coffey C et al., 2003; Hines LA et al., 2016; Hindocha C et al., 2015; Chen C-Y, O'Brien MS and Anthony JC, 2005) Males typically have an earlier opportunity to use cannabis, a greater risk of dependence and a faster progression from first opportunity of use to dependence. (Coffey C et al., 2003; Hines LA et al., 2016) These findings are consistent with normative data from European treatment services: the mean age at first cannabis use is 16, the mean age of first treatment is 24, and 83 % of treated individuals are male. (European Monitoring Centre for Drugs and Drug Addiction, 2015)

Interestingly, a three-year prospective study of daily users found that variables related directly to cannabis use did not predict transition to dependence; more important were current factors such as living alone, coping motives and negative life events (such as having had a major financial crisis). (Van der Pol P et al., 2014). A meta-analysis of 24 twin studies suggested that genetic influences account for 55 % of the vulnerability to cannabis dependence, with shared environmental factors and non-shared environmental factors accounting for much lower proportions (17.5 % and 27.5 %, respectively). (Verweij KJ et al., 2010)

Cannabis, anxiety and depression

Like most dependencies, cannabis dependence is often comorbid with other mental health problems. Epidemiological evidence indicates a possible association between regular cannabis use and the development of anxiety and depression. However, the evidence is more mixed and less consistent than that between cannabis use and psychosis. (Moore et al, 2007) One recent study compared the mental health of individuals who were dependent on cannabis

(according to the *DSM-IV*) with that of non-dependent cannabis users who had similar patterns of cannabis use. Only the dependent users had depression and anxiety problems (Van der Pol et al., 2013). Studies of young (16–24-year-old) daily cannabis users have found that levels of THC in hair are significantly associated with self-reported levels of both depression and anxiety (Morgan C et al., 2012).

The interconnectedness of cannabis use, mental-health problems and cognitive functioning is important. It is inherently difficult to determine causality in the type of studies discussed above because factors besides cannabis use (e.g. premorbid cognitive and emotional function) may be directly associated with risk of mental illness. Such factors could predispose an individual both to mental illness and to using cannabis, and the combination of these disorders would in turn increase their impact upon cognitive functioning.

Cannabis and psychosis

Nearly 2,000 papers have been published on this topic since 1962, and the pro-psychotic effects of cannabis have dominated media reporting about this drug. But how clear is the link? A number of longitudinal, population-based studies show an earlier first episode (Large M et al., 2011) and a roughly two-fold increase in risk of psychosis with regular cannabis use (Moore TH et al., 2007). Yet the vast majority of people who use cannabis do not develop psychotic disorders and many people diagnosed with such disorders have never used cannabis.

More agreement is found in evidence that heavy cannabis use may mean that young people who are vulnerable to psychosis develop the disorder when they may not have otherwise done so. Converging data suggest that this may have a genetic basis, with certain polymorphisms of the gene encoding AKT1 potentially conferring risk of psychosis following smoking cannabis acutely and chronically. (Morgan CJA et al., 2016; Di Forti M et al., 2012; Van Winkel R et al., 2011).

The type of cannabis used has recently been found to impact on risk of psychosis: self-reported hash use, even daily, is not associated with increased risk of psychosis, whereas self-reported daily use of skunk (which contains high levels of THC and negligible amounts of CBD) is associated with a five-fold greater chance of having schizophrenia (Di Forti M et al., 2015). Several studies using objective biological markers of use have shown that CBD reduces the psychosis-like effects of THC (Morgan C and Curran HV, 2008; Morgan C et al., 2011)

How cannabis interacts with the brain to increase psychosis risk is unclear. Disruptions in the brain's endocannabinoid system have been found in psychosis and may provide clues as to the pro-psychotic impact of cannabis. Anandamide is a naturally occurring CB-receptor agonist. Higher levels of anandamide in the cerebrospinal fluid have been associated with lower psychotic symptoms in individuals diagnosed with schizophrenia in individuals classified as having prodromal schizophrenia who do not smoke cannabis and in cannabis users without a diagnosis of schizophrenia. (Leweke FM et al., 1999; Koethe D et al., 2009; Morgan CJ et al., 2013) Anandamide is known to have a neuromodulatory role in

the brain; thus, during prodromal or first-episode psychosis, anandamide may be increased to attempt to control dysregulated brain dopamine. (Di Marzo V, 2008)

8. Therapeutic applications and extent of therapeutic use

The place of cannabis/cannabinoids in medical care

Cannabis and its derivatives may have a place in the treatment of three difficult conditions: chronic pain including fibromyalgia, chemotherapy induced nausea and vomiting, and the symptoms of multiple sclerosis.

All these conditions can be challenging for the clinician to manage; existing therapies have limited effectiveness. In chronic pain, around one person in six will respond to antidepressants or antiepileptics. Opioids are frequently tried but are largely ineffective despite high doses. Neuropathic pain caused by HIV/AIDS or chemotherapy remains extremely resistant to any treatment. Nausea and vomiting for highly emetogenic chemotherapy regimens is very difficult to manage and is distressing for patients. Similar problems exist in managing the symptoms, especially spasm, for multiple sclerosis sufferers.

In all of these conditions, there may be a role for standardized cannabis based products.

Evidence of effectiveness

Many organizations including WHO use a hierarchy of evidence to support or deny the use of certain medicines. Systematic reviews of randomized controlled trials (RCTs) or large RCTs are considered the highest level.

Searches were carried out up to the end of August 2016 using Medline, Embase, the Cochrane Library and the IACM database. Studies involving healthy volunteers have not been considered.

An extensive search of the medical databases using a variety of terms for cannabis and its derivatives identified nine good quality systematic reviews for seven areas of medicine namely:

- chemotherapy induced nausea and vomiting,
- chronic pain,
- dementia,
- fibromyalgia,
- rheumatoid arthritis,
- symptoms of HIV/AIDS, and
- treatment of spasticity in multiple sclerosis.

When describing these studies, it is not always easy to distinguish between cannabis, its preparations (e.g. nabiximols) and other cannabinoids (e.g. dronabinol, which is a constituent

of cannabis, but has also its own listing in the United Nations Convention on Psychoactive Substances). Moreover, some synthetic cannabinoids, such as nabilone, are sometimes included in the study designs.

The IACM database contained two review articles (not strictly systematic) for clinical studies published between 2005 and 2009 and 2010-2014. (IACM database, website) A search of the Central database of the Cochrane Library (search date 23.8.16) produced 1142 studies tagged as RCTs. (Cochrane Library, website)

Systematic reviews

These are briefly described to show that there is a good evidence base in some conditions for the medicinal use of cannabis derivatives.

1. Chemotherapy induced nausea and vomiting.

Two reviews described the use of cannabis derivatives or smoked cannabis for treating nausea and vomiting.

The first by Machado published in 2008 included 30 RCTs (1,719 participants). It concluded that dronabinol was statistically and clinically more effective than neuroleptics with an Number Needed to Treat (NNT) of 3.4 to prevent one episode of vomiting (A NNT closer to one is better, a higher NNT is worse). They concluded that the synthetic cannabinoids levonantradol and nabilone were not superior to neuroleptics. (Machado Rocha FC et al., 2008)

A later Cochrane review by Smith in 2015 included 23 RCTs (1326 participants) using stricter inclusion criteria than Machado. The review showed that cannabinoids were superior to placebo but there was no difference in efficacy between cannabinoids and prochlorperazine. In that scenario, participants reported a preference for cannabinoids in cross-over studies. (Smith LA et al., 2015)

2. Chronic pain

Two reviews examined evidence for chronic pain and neuropathic and multiple sclerosis (MS) related pain. (Martin-Sanchez E et al., 2009; Iskedjian M et al., 2007)

The review by Martin-Sanchez et al. looked at chronic pain of greater than six months assessing cannabis preparations administered by any route compared to a placebo group. Eighteen RCTs (809 participants) were included. The trials showed a significant reduction in mean pain scores but also an increase in CNS related adverse events specifically euphoria, altered perception, motor function or cognitive function but not dysphoria. (Martin-Sanchez E et al., 2009)

The second review by Iskedjian published in 2007 included seven RCTs (298 participants) of cannabis derivatives for MS related pain or similar neuropathic pains. Cannabis preparations were more effective than placebo in reducing pain scores with the

largest reduction achieved with cannabidiol/THC buccal spray (nabaximols). Cannabidiol and dronabinol separately also showed effectiveness. Dizziness was the most commonly reported adverse effect. (Iskedjian M et al., 2007)

3. Dementia

This Cochrane review published in 2009 by Krishnan et al. identified one study of 15 participants. The authors concluded that there was a lack of evidence to support the use of cannabinoids for dementia. (Krishnan S et al., 2009)

4. Rheumatoid arthritis (RA)

Just four RCTs of 141 participants were included in a Cochrane review by Richards et al. published in 2012. The authors looked at neuromodulators for pain management in RA. One small low quality trial of 58 participants assessed oromucosal cannabis against placebo and found a small significant difference in reduction of pain. (Richards BL et al., 2012) However the study is too small to be reliable.

5. Symptoms of HIV/AIDS

Another Cochrane review by Lutge et al. looked at the use of cannabis for reducing morbidity and mortality in HIV/AIDS. Seven studies (330 participants) were included but the studies were small and of short duration and failed to show benefit. (Lutge EE et al., 2013)

6. Treatment of spasticity in multiple sclerosis

A review by Lakhan et al. in 2009 included 6 RCTs (820 participants). The intervention was a combined extract of THC and cannabidiol. The studies showed a reduction in spasticity and improved motility in patients with MS. The authors report that adverse effects were generally well tolerated. (Lakhan SE and Rowland M, 2009)

A Cochrane review by Mills et al. published in 2007 specifically looked at treatments for ataxia in MS. Ten studies of different interventions were included but only 2 studies (29 participants) used cannabis making it impossible to draw any meaningful conclusions. (Mills RJ et al., 2007)

Primary Studies

1. The IACM database (IACM database, website)

Two review articles published in the journal 'Cannabinoids' cover the time period from 2005 to 2014 in separate papers. Combining the tables (Table 2) gives a good indication of the size of the literature around the use of cannabis and related products in various conditions. Six small studies (125 participants) examined the use of smoked cannabis and two studies (344 participants) reported on studies of oral cannabis extract (herb).

Table 2. Overview of the size of the literature around the use of cannabis and related products in various conditions

Condition	No of studies	Total no of participants
Chronic and /or neuropathic pain	22	1842
Multiple sclerosis	15	2815
HIV/AIDS	4	118
Irritable bowel syndrome	3	133
Nausea and vomiting	3	246
Other conditions	16	438

2. Central database of the Cochrane Library (Cochrane Library, website)

Seventy two studies of the medicinal use of cannabis were identified on the Central database out of over 1000 citations. The remainder generally describe studies dealing with dependence related issues. Six studies describe the use of smoked or vaporized cannabis with five in patients with chronic neuropathic pain (166 participants) and one in multiple sclerosis (37 participants). All small studies report a significant reduction in pain intensity compared to placebo.

Extent of therapeutic use

Currently, medical use of cannabis is allowed in a number of countries. In 2000, total production was 1.3 tonnes; by 2014 it had increased to 56.9 tonnes. (International Narcotics Control Board, 2015) The main producer countries (2012) are Canada (75 % of the global production), the United Kingdom (18 %) and Israel (5 %). (International Narcotics Control Board, 2014) Table 3 presents the actual legal consumption for 2014 as reported by the countries to INCB. This is mainly for medical purposes, but also includes research. It should be noted that not all countries submitted their reports.

Table 3. Legal cannabis consumption by country in kg (2014) (International Narcotics Control Board, 2015)

Canada	48,649	Spain	14
Israel	5,483	United States	11
United Kingdom	2,230	Hungary	3
Italy	548	Bulgaria	2
Netherlands	316	Czech Republic	2
Switzerland	72	Lithuania	2
Austria	49	Germany	1
Portugal	28	Gibraltar	1
Denmark	15		

In the United States, the states of Alabama, Alaska, Arizona, California, Colorado, Connecticut, Delaware, Florida, Hawaii, Illinois, Iowa, Kentucky, Louisiana, Maine,

Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Washington, Wisconsin, Wyoming and the District of Columbia approve and regulate the medical use of cannabis, although it remains prohibited under federal law. (NORML, website)

9. Listing on the WHO Model List of Essential Medicines

Not listed.

10. Marketing authorizations (as a medicine)

Sativex® (GW Pharmaceuticals plc., Cambridge, United Kingdom; marketed by Bayer) is a standardized extract of cannabis (nabiximols USAN). This is a mixture of two cannabis extracts containing fixed concentrations of dronabinol and cannabidiol. Each ml contains 38-44 mg and 35-42 mg of two extracts (as soft extracts) from Cannabis sativa L., folium cum flore (Cannabis leaf and flower) corresponding to 27 mg delta-9-tetrahydrocannabinol and 25 mg cannabidiol. Additional constituents include related cannabinoids and non-cannabinoid components in small amounts. It is provided as oromucosal spray. A unit dose is 100 microlitres sprayed into the mouth, giving a dose of 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol.

The cannabis is produced and extracted in the United Kingdom. Sativex® is licensed as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

Sativex® has been approved as a medicine in 28 countries (including Austria, Australia, Belgium, Canada, the Czech Republic, Denmark, Finland, Germany, Hungary, Iceland, Ireland, Israel, Italy, Luxemburg, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom).

Sativex® is also in Phase 3 for the indication of treatment of cancer pain.

Dronabinol (INN) is a constituent of cannabis which is separately controlled under the UN Convention on Psychotropic Substances. Dronabinol has been reviewed previously by the ECDD, for the last time in 2007. (World Health Organization, 2006a; World Health Organization, 2006b) It is also a constituent of the medicine Marinol® (2.5 mg, 5 mg, 10 mg), which is marketed by AbbVie and licensed in the USA and Canada for management of the loss of appetite associated with weight loss in acquired immune deficiency syndrome (AIDS) and management of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments. The dronabinol in Marinol® is semi-synthetic, as it is prepared by extracting cannabidiol from cannabis low on dronabinol and then converted into dronabinol. (This is related to the controls on the cultivation and handling of cannabis high on dronabinol)

At least three more companies have four new preparations in the pipeline:

1. Echo Pharmaceuticals (Weesp, the Netherlands) developed a THC-based product, which is in Phase III for multiple sclerosis and in Phase II for Alzheimer's disease and chronic pain.
2. Echo developed a CBD-based product which is in Phase II for schizophrenia. (cho Pharmaceuticals, website)
3. Syqe medical (Tel Aviv, Israël) developed two types of single-dosage inhalers, one of which has selective 100 microgram dosing precision, the other producing a THC pharmacokinetic profile with low-interindividual variation of C_{max}. See also the Subsection Pharmacokinetics of inhaled cannabis. (SYQE Medical, website)
4. Axim Biotechnologies, Inc. (New York NY, USA) is in the process of developing a chewing gum containing cannabinoids for multiple sclerosis and chronic pain and expects registration second half of 2018. Clinical trials are conducted together with Free University Amsterdam. Research with various other cannabinoid-based preparations are ongoing. (Axim Biotech, website)

11. Industrial and other use

Industrial and agricultural uses

As discussed above, hemp is used for its fibers. Examples of this use are the manufacturing of rope, carbon fiber materials (e.g. for car dashboards) and insulation materials. Hemp straw is used for covering horse stable floors.

(The materials used in these applications are outside the Convention's definition of cannabis)

Nutritional uses

Hemps seeds are used as such in bread or are pressed for the production of vegetable oil. Hemp seed oil has a high content of polyunsaturated fatty acids. If rinsed with water, the seeds contain only traces of tetrahydrocannabinol. (The seeds if not accompanied by the flower buds are outside the Convention's definition of cannabis)

Religious uses

Cannabis serves as a sacrament in various religions, a few of these are the Rastafari movement (Jamaica) and the Church of Santo Daime (Brazil).Wikipedia mentions at least 16 more religions using cannabis. (Wikipedia, website**)**

The Rastafari movement, a religion which started in the 1930s in Jamaica, uses cannabis ("Ganja") in a highly ritualized manner during the religious ceremonies. Their focus is not on getting high. The use of cannabis during these ceremonies is based on the believe that the Tree of Life mentioned in the Bible is cannabis and that several other biblical passages further promote its use, such as "Thou shalt eat the herb of the field" (Genesis 3:18), "Eat every herb of the land" (Exodus 10:12) and "The herb is the healing of the nations"

(Revelation 22:2). (Dufton E, 2015) (The religious uses of cannabis are inside the Convention's definition of cannabis)

12. Epidemiology of non-medical use and dependence

Cannabis is the most commonly used illicit drug. Globally around 182 million people (15-64 years old) used cannabis in 2013 for non-medical reasons. (United Nations Office on Drugs and Crime, 2015a) There are marked variations across WHO regions in the recorded prevalence of cannabis use, and in how and how often countries collect this data. In the USA a recent survey (N=596,500) showed cannabis use by adults increased from 10.4 % in 2002 to 13.3 % in 2014 and this change was associated with a decrease in the perception of risk of using the drug 1-2 times per week. However, it is noteworthy that there was no increase in cannabis use disorders which remained around 1.5 % across the years. (Compton M et al., 2016) In the European Region, it was estimated that 16.6 million young people (15-34 year olds) used cannabis in the last year which corresponds to 11.7 % of this age group. (European Monitoring Centre for Drugs and Drug Addiction, 2016) Of the adult population (15-64 year olds) in Europe, 22.1 million (6.6 %) used the previous year and 83.2 million 24.8 % used in their lifetime. (European Monitoring Centre for Drugs and Drug Addiction, 2016) There is considerable variation across countries in cannabis use (e.g. lifetime prevalence by 15-24 year olds is over 40 % in France, the Czech Republic and Denmark but less than 10 % in Greece, Malta and Romania. (European Monitoring Centre for Drugs and Drug Addiction, 2016) As with other drugs, rates of cannabis use are more than twice as high in men than in women and higher in more urban, densely populated areas. Similarly, like other illicit substances, use is highest among 15-24 year olds, with 16 being the median age of first use of cannabis in most European countries. (cf. Curran et al. HV, 2016).

The chances of becoming dependent on cannabis after lifetime exposure is 8.9 %, which is considerably lower than for alcohol (22.7 %), tobacco (67.5 %) or cocaine (20.9 %). (Lopez-Quintero C et al., 2011) At the same time, the clinical need for treatment of cannabis dependence is substantial and increasing in North America, Europe and Oceania. (United Nations Office on Drugs and Crime, 2015.) Across Europe, cannabis now accounts for more first-time entrants to drug treatment services than any other illicit drug, reflecting the greater prevalence of use of cannabis than other illicit substances. (European Monitoring Centre for Drugs and Drug Addiction., 2015) One study estimated that 1.8 % of 14-17 year olds in Europe meet clinical criteria for cannabis dependence. (Wittchen H-U et al., 2011)

The majority of even daily cannabis users do not become dependent on the drug. A prospective study of 600 18-30 year old daily or near daily cannabis users in the Netherlands found 37.2 % fitted dependence criteria over a 3 year assessment period. (Van der Pol P et al., 2013) However, what predicted transition to cannabis dependence were those young people's current problems (e.g. living alone, coping motives for cannabis use, number and type of recent negative life events) and not the extent of cannabis use.

13. Nature and magnitude of public health problems related to non-medical use and dependence

Mental health problems are the major public-health concern with cannabis. These are cannabis dependence, increased risk and earlier onset of psychosis and depression (see previous sections on these). Driving while under the influence and respiratory problems from smoking are other public-health concerns.

Driving

Numerous laboratory studies have shown that acute cannabis or THC dose-dependently impair concentration, reaction time and perceptual-motor co-ordination. These impairments are more marked in occasional than regular cannabis users. Epidemiological studies indicate that cannabis users who drive when intoxicated double their risk of a car crash (Asbridge et al., 2012). This risk increases significantly if drivers also have elevated alcohol levels (Hartman & Huestis, 2013). One of the biggest research projects ever carried out in 9 EU countries on drugs and driving found that 2 ng/ml THC in whole blood (3.8 ng/ml THC in serum) caused impairment equivalent to 0.5 g/l BAC which is the legal limit for driving in many countries. (European Monitoring Centre for Drugs and Drug Addiction, 2012b) There is evidence that cannabis users adapt their driving behaviour when under the acute influence of the drug and become more cautious. Overall, the existing evidence points to a small causal impact of cannabis on injury through traffic accidents. (World Health Organization, 2016) The effect is particularly small compared to that of alcohol.

Respiratory problems

A number of studies have investigated whether smoking cannabis increases the risk of chronic obstructive pulmonary disease (COPD). Most have found that although the risk of chronic bronchitis is increased, there is no increased risk of COPD. Cannabis-only smokers are more likely to report cough, sputum and wheezing than controls who do not smoke and those who subsequently quit using the drug show reductions in those same symptoms compared with those who continue use. (Tashkin DP, Simmons MS and Tseng CH, 2012; World Health Organization, 2016) In many parts of the world, cannabis is smoked mixed with tobacco and this renders the user subject to the many negative health risks of tobacco smoking.

14. Licit production, consumption and international trade

Non-medical use

In 2014, Uruguay legalized the production and use of cannabis for medical and non-medical purposes. Individuals need to register with a state agency, the Institute for Regulation and Control of Cannabis (IRCCA). They can choose from three ways to obtain their cannabis:

a. They can purchase up to 40 grams in licensed pharmacies with or without a prescription. The cannabis is produced by a number of commercial state-licensed growers;

b. They can grow up to six female flowering cannabis plants per household for their own consumption, after registering their plants with the IRCCA. The total annual production of the drug must not exceed 480 grams; or
c. They can join cooperatives to collectively grow cannabis with others. These "cannabis clubs" must be registered with the IRCCA and other authorities, and must have between 15 and 45 members. (R Walsh J and Ramsey G, s.a)

Medical use

Cannabis is cultivated in a number of countries for the production of medicines. In the United Kingdom, it is produced for the production of Sativex®, although medical use of the herb as such is not allowed in this country.(See Section 12)

In many other countries the medical use is permitted as described in Section 9

"Cannabis flos" is on the market as a pharmaceutical starting material in the Netherlands. Starting materials do not need a marketing authorization, but can be legally used for compounding in pharmacies, or dispensed as such, which is more often the case for herbs, but also for some chemicals e.g. magnesium sulphate crystals as a laxative. Most cannabis is dispensed just as the dried herb, but at least one pharmacy prepares oily drops for oral administration.

The Dutch company Bedrocan BV produces for the Dutch Ministry of Health, Welfare and Sport, but also holds a branch in Canada. The Dutch branch has GMP status. It produces six standardized varieties:

- Sativa types:
  - Bedrocan® (THC: 22 %, CBD: <1 %),
  - Bedrobinol® (THC: 13,5 %, CBD: <1 %) and
  - Bediol® (THC: 6.5 %, CBD: 8 %);
- Indica types:
  - Bedica® (THC: 14 %, CBD: <1 % and presence of terpenes, e.g. myrcene) and
  - Bedropuur® (THC: 20 – 23 % , CBD: <1 %, only available in Canada and for research purposes);
- A non-psychoactive strain: Bedrolite® (approximately 9 % CBD and 0.4 % THC).

A placebo variety by Bedrocan BV is also available.

Bediol® and Bedica® are marketed in granulated form (i.e. chopped, max. particle size 5 mm). The cannabis is pharmacy only and prescription only. (Bedrocan, website) Usually it is administered as a herbal tea or by inhalation after vaporization. (Ministry of Health, Welfare and Sport, Information video) The Dutch Office of Medicinal Cannabis is willing to deliver also outside the Netherlands if the authorities of that particular country agree to that.

In Canada, 35 producers have been licenced (as per September 2016). (Health Canada, website) All licensed producers are subject to inspections by Health Canada to verify compliance with the requirements of Marihuana for Medical Purposes Regulations Controlled Drugs, the Controlled Drugs and Substances Act (CDSA) and its regulations, as well as the Food and Drugs Act (FDA) and its regulations. This also includes meeting the requirements of Good Production Practices (GPP), which include standards for microbiological and chemical contamination, testing for tetrahydrocannabinol and cannabidiol contents, which pest control products are permitted, and maximum residues of such products. (Health Canada, 2013) Importation and exportation is possible.

Other countries permitting or considering to permit medical use of cannabis include Australia, Brazil, Colombia, Croatia, the Czech Republic, Denmark, Italy, Jamaica, Macedonia and Poland.

15. Illicit production and traffic, and related information

The World Drug Report 2016 provides detailed information about the production and traffic of cannabis herb and resin world-wide.

Cannabis plant cultivation was reported on the territory of 129 countries over the period 2009-2014. Given the absence of systematic measurements, however, the extent and trends in cannabis cultivation and production are difficult to assess. Most indirect indicators come from law enforcement authorities and, to a certain extent, reflect their priorities and activities and not simply the existence of cannabis cultivation and production.

Since 1998, the total area of eradicated cannabis plants has decreased, as have seizures of cannabis plants. These trends contrast with seizures of cannabis herb and cannabis resin, which, after a twofold increase over the period 1998-2004, have remained largely stable.

Reports from Member States on source countries for cannabis resin during the period 2009-2014 suggest that the world's largest producer of cannabis resin continues to be Morocco, followed by Afghanistan and, to a lesser extent, Lebanon, India and Pakistan. Most of the world's production of cannabis herb takes place in North America, mainly Mexico and the United States, for consumption in the sub region, while hydroponic cultivation of cannabis plants seems to be concentrated in Canada and the United States.

Reports by Member States over the period 2009-2014 indicate that Albania, Colombia, Jamaica, the Netherlands and Paraguay are important source countries of the cannabis herb sold in international markets.

In 2014, the Americas accounted for about three quarters of all the cannabis herb seized worldwide (North America: 37 % of global seizures; South America: 24 %; the Caribbean: 13 %), Africa accounted for 14 % and Europe accounted for 6 %.

Despite an increase in cannabis use, the quantity of cannabis herb intercepted in North America, after reaching a peak in 2010, has been declining, reflecting the fact that a decrease in cannabis production has been reported in Mexico and that cannabis interdiction may have become less of a priority in the United States since the decriminalization and legalization of recreational use of cannabis in some of the states in that country. Nonetheless, the quantity of cannabis herb seized in other parts of the world, particularly in South America, the Caribbean and Africa, is actually on the increase

.

The sub region in which the largest amount of cannabis resin was seized in 2014 was again Western and Central Europe, accounting for 40 % of the global seizures of cannabis resin; 32 % of the world total was accounted for by countries in North Africa (mainly Morocco and Algeria) and 25 % was accounted for by countries in the Near and Middle East (mainly Pakistan, followed by the Islamic Republic of Iran and Afghanistan). (United Nations Office on Drugs and Crime, 2016)

The EMCDDA report on cannabis describes how cultivation and traffic over decades changed from a rather individual and small scale undertaking in the 1960s to a highly professional and large scale operation with the involvement of organized crime. Moreover, cocaine importation now benefits from the infrastructure for cannabis importations

In Europe, the resin has been replaced by the herb that is produced in Europe itself or imported, with a great variety in types of herbal cannabis and both indoor and outdoor cultivation. (European Monitoring Centre for Drugs and Drug Addiction, 2012a)

16. Current international controls and their impact

Scheduling

Cannabis is scheduled in the Single Convention on Narcotic Drugs in both Schedule I and IV. This combination is the strictest control possible under the Conventions.

Additional controls specific for cannabis and cannabis resin

In addition to the control measures required because of the scheduling in Schedules I and IV, the Single Convention contains controls in the provisions of Article 28, paragraph 1. Like for the other two crops regulated in the convention in this way (the poppy plant and the coca plant), there is a system of state controls in case a country allows the cultivation of the plant. The controls include that a government agency is established designating the area where cannabis can be cultivated, licensing the cultivators and purchasing and collecting the crops within four months after the harvest. This agency also will have the exclusive right of importing, exporting, wholesale trading and maintaining stocks. Article 28 prescribes these provisions by referring to Article 23, where similar controls for the cultivation of the poppy plant are provided. The controls of cannabis cultivation should be analogous to the controls of the cultivation of the poppy plant, which are described in detail.

Article 28, paragraph 2 points out that "[t]his Convention shall not apply to the cultivation of the cannabis plant exclusively for industrial purposes (fibre and seed) or horticultural purposes." Horticultural purposes are e.g. the use as wind screens in horticulture.

Article 28, paragraph 3 requires that countries "adopt such measures as may be necessary to prevent the misuse of, and illicit traffic in, the leaves of the cannabis plant."

Although the title of Article 3 of the Convention is "Changes in the Scope of Control", the text of this article relates only to changing the scheduling. As Article 28 is part of the text body of the convention, and not a consequence of the scheduling, the World Health Organization mandate to make recommendations on the controls from Article 28 is only implicit.

Consequences of the horticultural and industrial exemption

The exemption for horticultural and industrial purposes is defined in the Convention in terms of how the cultivated plants will be used, and not by their content of the active constituent. This provides a way out for illicit cultivation by pretending that the purpose is horticultural or industrial. For this reason some countries use instead an upper limit of tetrahydrocannabinol (e.g. in the EU, approved cannabis varieties with a content no higher than 0.9 % tetrahydrocannabinol) As this example clearly illustrates, limiting the tetrahydrocannabinol content instead of defining the purpose of the cultivation can result in more effective control and more legal certainty for the grower of cannabis plants.

It would therefore make sense for the Committee to consider recommending an exemption by tetrahydrocannabinol content instead of the current exemption based on the purpose the product is intended for. Such a recommendation would be to designate certain hemp varieties with a known average tetrahydrocannabinol content not higher than a certain percentage under which no significant psychoactive effects of the hemp is to be expected.

However, such a change in the scope of control will require amendment of the text body of the Single Convention, something that may be much harder to achieve than amendment of the schedules.

The impact of current international controls

Today, many countries face problems from the strict enforcement of the prohibition as prescribed by the Conventions:

The main ones are:

- friction with other international treaties, such as infringement of religious and indigenous rights;
- many countries have high imprisonment rates for small drug offences, including the possession of cannabis for own consumption and those who have once been imprisoned have considerable problems to take up their lives after their release;

- human right violations occur as collateral damage, e.g. when wells for drinking water for the population or for cattle nearby illegal crops are poisoned from spraying herbicides; etcetera.
- The regulations controlling cannabis as Schedule 1 severely hamper research into both medical and scientific questions. (Nutt DJ, King LA and Nichols DE, 2013)

In some countries specific population groups suffer heavily under the prohibition, whilst other groups a relatively left alone by the authorities. Currently, in the Philippines, drug control has given rise to extrajudicial killings after a call by the newly elected president Rodrigo Duterte on the police and the population, who announced that he will have 3 million people killed..

In recent years, the world has seen the rise of synthetic cannabinoids largely in an attempt to get around the legal restrictions on herbal cannabis products. Most of these are untested and many are much more potent than the plant products.

In its thirty-sixth meeting, the Committee reviewed six new synthetic cannabinoids and recommended the scheduling of two of them, (World Health Organization, 2015) The Critical Review Reports of JWH-018 and AM-2201, which were then recommended for scheduling, reported deaths attributed to the use of these substances. (World Health Organization, 2014a; World Health Organization, 2014b). On the agenda of the 38th meeting of the Committee are again four synthetic cannabinoids listed for Critical Review.

The prevalence of synthetic cannabinoids use is difficult to estimate at a global level as data from drug use surveys is only available for some countries. In 2013 and 2014, synthetic cannabinoids were the largest group of new psychoactive substances (NPS) reported. Newly introduced synthetic cannabinoids are usually not (yet) prohibited and by trafficking new synthetic cannabinoids instead of cannabis, drug traffickers evade the prohibition of cannabis. Their marketing as 'herbal products' that produce experiences similar to cannabis seems to have increased their popularity as "legal cannabis substitutes", however, they are perceived, in many cases correctly, as more dangerous. (United Nations Office on Drugs and Crime, 2016; United Nations Office on Drugs and Crime, 2015b)

Apparently in a partially illicit and partially licit market, there is a relationship between cannabis and synthetic cannabinoids. Therefore, it may be assumed that international controls on cannabis and cannabis resin have an impact on the availability of synthetic cannabinoids. However, according to UNODC, it was (2015) too early to assess this impact of synthetic cannabinoids on the cannabis market.(United Nations Office on Drugs and Crime, 2015b)

Another problem resulting from the prohibition of cannabis for medical use (scheduling in Schedule IV) is the difficulty in organizing clinical trials. Often the authorities do not issue the licences needed for this, based on the fact that the treaty implementation at the national level does not allow such trials. In the case of multi-centre randomized clinical

trials this is even more difficult. In this way the scheduling in Schedule IV has for a long time been both cause and effect: the scheduling was an impediment for clinical trials and the limited evidence was a reason for maintaining prohibition on clinical trials. (Personal experience of several of the authors throughout their careers) In spite of this, scientists in some countries were able over time to build considerable evidence for the clinical efficacy as described elsewhere in this report. However, in most cases it has been difficult or impossible to conduct such trials with standardized and reproducible cannabis batches.

17. Current and past national controls

Non-medical use

For many decades, the control of cannabis was in most or all countries in line with the Single Convention (see Section 18, Current international controls and their impact). However, the impact of controls has led to a situation where more and more countries regulate cannabis in a flexible way and even, in some cases, lift the prohibition of use and trade in order to reduce the problems resulting from prohibition.

Non-medical use is or will be soon legal in Uruguay and four states of the United States.

In Washington and Colorado, legally taxed and regulated cannabis markets were adopted in voter ballots in 2012, followed by similar initiatives in Alaska and Oregon in 2014. Washington DC legalized the possession and home cultivation of cannabis. Recent reports on cannabis use among adolescents in these two states do not show an increase. (Colaneri N et al., 2016; Healthy Kids Colorado Survey, 2015)

Uruguay regulated the cannabis market legally in 2013, granting the government control over the import, export, cultivation, production, and sale of cannabis through the newly established Institute for the Regulation and Control of Cannabis (Instituto de Regulación y Control del Cannabis, IRCCA). (United Nations Office on Drugs and Crime, 2016)

Canada's 2015 elected government announced that it will introduce legislation to legalize and regulate cannabis for non-medical, non-scientific use in Spring 2017. (Anonymous, 2016)

Uruguay has argued that its policy is fully in line with the original objectives that the drug control treaties emphasized, but have subsequently failed to achieve - namely, the protection of the health and welfare of humankind. Uruguayan authorities have specifically argued that the creation of a regulated market for adult use of cannabis is driven by health and security imperatives and is therefore an issue of human rights. However, the INCB has made clear statements that both Uruguayan and U.S. cannabis regulation models are not in compliance with the treaties.(Anonymous, 2016)

A large number of countries have not lifted the prohibition itself, but found other ways to mitigate the negative impact of the implementation of the controls required for cannabis. Since the early 1970s, some countries adapted the regimen to their needs, e.g. by decriminalizing, condoning or legalizing the possession of cannabis and sometimes also the distribution and production.

In the Netherlands, the 1976 revision of the Opium Act introduced the distinction between "hard" and "soft" drugs, the former having unacceptable risks, the latter not carrying such risks. Cannabis and cannabis resin were classified as soft drugs. Simultaneously, the possession of 5 gram of cannabis or less was condoned, as well as (under certain conditions) the sales of such amounts by "coffee shops". However, the supply to these coffee shops continues to be prohibited and constitutes a continuous friction in the country's drug policies. More recently, some courts refused to convict those involved in the supply of cannabis to coffee shops, reasoning that the policy of condoning sales implies that there is a condoned supply as well.

In Denmark, possession of less than 10 gram was not prosecuted from 1969 until 2004, with the turning of "a blind eye" to small-scale sales. In 2004 after the possession was "re-criminalized", street dealing emerged all over Copenhagen and the market-related violence of criminal gangs disputing control over selling points increased, including fatal shootings. In the five-year period after the crackdown there were more homicides and attempted homicides in Denmark than in any five-year period in the previous 20 years. (Blickman T, 2014)

In Portugal under a law from 2001, possession and purchase of illicit drugs for personal use is an administrative offence and people found to possess drugs, including cannabis, are sent to a Drug Addiction Dissuasion Commission of the Ministry of Health. (Informal Drug Policy Dialogue, 2011)

Other countries tend to adopt the "Cannabis Social Club" model. This is a model of collectively growing cannabis for personal use. Although these clubs are not formally legal in any country at the moment, they are condoned in Spain. In some European cities they have the support of local authorities. (Blickman T, Personal information)

Regulations for medical use

A listing of countries with licit production for medical purposes has been provided in Section 10 (Therapeutic applications and extent of therapeutic use). In most of these countries and states, no specific provisions are established to meet the requirement of Article 28 of the Single Convention that a state agency takes in the harvest and controls the distribution of the production.

The Netherlands established the Office of Medicinal Cannabis within the Ministry of Health, Welfare and Sport in 2001 to meet the requirement by law that the Minister makes sufficiently medical cannabis available for scientific and medical purposes.

The office is responsible for all the functions mentioned in the Convention. All actors in the production and distribution chain (except pharmacies) require a license and are contracted by the OMC. The medical cannabis is distributed as the inflorescences ("Cannabis flos") by a distributor company on behalf of the OMC. It can be dispensed to patients with a prescription. As Cannabis flos is on the market as a starting material, it can also be used by pharmacies for compounding preparations and at least one pharmacy uses it to make oily drops, which allows for more easy dosing by the patient.

In the United States, the National Institute on Drug Abuse (NIDA) is the national agency according to Article 28. However, it is only the production for scientific purposes that is controlled by NIDA; it does not interfere with the production in the states that legalized cannabis. In those states that allow medical use of cannabis, local regulations are implemented that regulate who can have access and how.

In Canada, the Access to Cannabis for Medical Purposes Regulations provide a framework for commercial production by licensed producers responsible for the production and distribution of quality-controlled fresh or dried marijuana or cannabis oil or starting materials (i.e., marijuana seeds and plants) in secure and sanitary conditions. These regulations also include provisions for individuals to produce a limited amount of cannabis for their own medical purposes or to designate someone to produce it for them. Individuals with a medical need, and who have the authorization of their health care practitioner, can access cannabis in three ways: they can register with licensed producers, they can register with the Ministry of Health to produce a limited amount for their own medical purposes, or they can designate someone else to produce it for them. (Health Canada, 2016)

A few more countries recently decided to allow medical use, including Jamaica and Colombia, and this list is still growing.

18. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Contamination hazards and quality control[3]

Where there is no government control over the cultivated medicinal cannabis, producers do not necessarily apply basic Good Production Practices like GAP, GMP, GLcP and GDP practices. This has consequences for the safety and efficacy of the medicinal cannabis:

- there can be considerable batch-to-batch variation in strength and the qualitative composition of the medicine, resulting in varying effectiveness.
- cannabis is known for containing *Aspergillus* fumigatus L., a fungus that can infect the user and produces toxins that may provoke a psychosis. A Dutch study compared

[3] The following part of this section is based on a document prepared by the author for the 36th Meeting of the Expert Committee on Drug Dependence.

illegal cannabis batches with medicinal cannabis produced under state control. Some samples of the former contained up to 480,000 colony forming units (CFU)/gram, while the latter was microbiologically safe (total aerobic microbial count of <10 CFU/g, total yeast and mould count of <10 CFU/g, and absence of Pseudomonas aeruginosa, Staphylococcus aureus, and bile-tolerant gram-negative bacteria). (Hazekamp A et al., 2005)

- contamination can also derive from pesticides used during production or from heavy metals in the substrate (e.g. from rock wool).

An example of production with good quality assurance is the Dutch medicinal cannabis. This is produced under responsibility of the Ministry of Health and meets a number of quality requirements: consistent strength of tetrahydrocannabinol and cannabidiol, consistent composition of secondary cannabinoids, absence of microbiological contamination, pesticides and heavy metals, and humidity. Where there is a norm provided in the European Pharmacopoeia, this norm is followed. (Office for Medicinal Cannabis, s.a)

More and more countries opt today for decriminalized, condoned or legalized production and distribution systems. However, in such systems, it is often the case that production/growing remains illegal and prone to prosecution. As a consequence, quality assurance for non-medical use of cannabis is not possible. Also in some countries where medical use of cannabis is permitted, production is often left in the hands of amateurs or other producers with no knowledge of requirements for pharmaceutical products.

It would be logical if quality assurance for commercialized non-medically used cannabis should be of equal level as that for food, e.g. by the usual quality assurance under HACCP (Hazard Analysis and Critical Control Points). Production would also be subject to similar surveillance by the authorities as food production.

For medical cannabis, quality standards should be higher than for recreational cannabis, because medical use requires a fixed dose-effect relation and patients need to be able to dose at a level below the psychoactive threshold. Also many patients are more vulnerable than the average person and some of them are immunocompromised, thus requiring microbiologically safe cannabis. Therefore, well defined products and full pharmaceutical quality control including GAP, GMP, GLcP and GDP practices is necessary with oversight by the health authorities.

Conclusions

Despite that the scheduling system of substances under the Single Convention on Narcotic Drugs is supposed to be based on scientific assessments, the WHO has *never* reviewed cannabis and cannabis resin. This means also that the Expert Committee continues to recommend that cannabis is not to be used medically despite growing evidence of considerable medical use world-wide, including the availability of a pharmaceutical preparation with a marketing authorization in multiple countries. Many countries are struggling with the impact of the prohibition of cannabis with its wide negative impact on societies (including through human rights violations) and on drug markets and drug use, including on the market of synthetic cannabinoids.

Committee recommendations are needed on the following topics:

1. Whether a Critical Review should be conducted for reviewing the current scheduling in Schedules I and IV. Each of the following reasons would justify a recommendation for a Critical Review:
   a. because WHO has never conducted a Critical Review, meaning that there is no scientific justification for the current scheduling;
   b. because the wide-spread medical use, including the use of preparations with a marketing authorization is in contradiction to listing in Schedule IV;
   c. because it is not clear whether the dependence-producing properties of cannabis and cannabis resin are between codeine and morphine (justification for Schedule I) or between dextropropoxyphene and codeine (justification for Schedule II) or below those of dextropropoxyphene (justification for not scheduling).

2. On the medical use of cannabis and its preparations (which can include revoking old recommendations by the Committee)

3. On the need of quality control on cannabis and cannabis products for medical and non-medical use.

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Declarations of Interest

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David Nutt is Professor of Neuropsychopharmacology at Imperial College London. He acts as an advisor to the British National Formulary psychiatric drugs section, the Medical Research Council the General Medical Council and the Department of Health. From 2000-2009 he was Chair of the technical committee of the UK Advisory Council on the Misuse of Drugs where he led several reports on cannabis as well as other drugs. He is currently President of the European Brain Council and in the past has been President of the British Association of Psychopharmacology, the British Neuroscience Association and the European College of Neuropsychopharmacology. He is the founding chair of DrugScience.org.uk a charity that communicates to the public the harms and benefits of legal and illegal drugs. He is a member International Centre for Science in Drug Policy, an advisor to Swedish government on drug, alcohol and tobacco research and for the past 25 years has been editor of the Journal of Psychopharmacology. He advises a number of pharmaceutical companies but none with an interest in cannabis products and has no share interests in any.

Willem Scholten, as an independent consultant, provides consulting services on the regulation of psychoactive substances and policies related thereto. This included speaking on accessibility of analgesia at conferences and meetings for the World Health Organization, Mundipharma and Grünenthal, and services such as providing an overview of importation and exportation rules, providing information on controlled substance policies, and assisting to the application of an International Nonproprietary Name. These have included work for PinneyAssociates, Grünenthal, Jazz Pharmaceuticals, and the World Health Organization. He represents the World Health Organization as a Member on the *Expert Group on framework and support measures for opioid dependence treatment including the prescription of agonist medicines* of the Pompidou Group of the Council of Europe. He participated in the *Expert Workshop on Cannabis Legalization and the Public Health* organized by the O'Neill Institute for National & Global Health Law, Georgetown University, Washington DC, USA and the Washington Office on Latin America (WOLA). He is a Member of the Board of Directors of International Doctors for Healthier Drug Policies.

Philip Wiffen runs a consultancy named Oxford Systematic Review Services. His work includes a review of the screening of athletes for cardiac conditions that may lead to sudden death and a consultation with a pharmaceutical company on fast acting over the counter pain medicines. None of his activities relate to the drafting of this report on cannabis.

About the authors

H. Valerie Curran is Director of UCL's Clinical Psychopharmacology Unit, Professor of Psychopharmacology and Research Lead at Camden & Islington's Drug Services. Her research spans a wide range of psychoactive substances which are used medically and/or for recreational purposes.

After grammar school in Manchester Val studied Natural Sciences at Cambridge University and completed her PhD at London University. She worked at the Institute of Psychiatry (from 1984) and also trained in clinical psychology before moving to UCL in 1996.

She has written 250 original scientific papers and many other publications including books and chapters. She has been a Principal Editor of the scientific journal, Psychopharmacology, for more than a decade.

Her research on cannabis started in 2002. It is funded mainly by the UK Medical Research Council and includes a current clinical trial to treat cannabis dependence. She recently first authored a review of cannabis (Keep Off the Grass: cannabis, cognition and addiction) which was published in *Nature Reviews Neuroscience, 2016*. A recent television documentary was made (by Channel 4) about her cannabis research: Drugs Live – 'The Cannabis Trial' 2015.is Director of UCL's Clinical Psychopharmacology Unit, Professor of Psychopharmacology and Research Lead at Camden & Islington's Drug Services. Her research spans a wide range of psychoactive substances which are used medically and/or for recreational purposes.

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documentary was made (by Channel 4) about her cannabis research: Drugs Live – 'The Cannabis Trial' 2015.

David Nutt is currently the Edmund J Safra Professor of Neuropsychopharmacology and Head of the Centre for Neuropsychopharmacology in the Division of Brain Science, Dept of Medicine, Hammersmith Hospital, Imperial College London. He is also visiting professor at the Open University in the UK and Maastricht University in the Netherlands.

After 11+ entry to Bristol Grammar he won an Open Scholarship to Downing College Cambridge, then completed his clinical training at Guy's Hospital London. After a period in neurology to MRCP he moved to Oxford to a research position in psychiatry at the MRC Clinical Pharmacology Unit where he obtained his MD. On completing his psychiatric training in Oxford, he continued there as a lecturer and then later as a Wellcome Senior Fellow in psychiatry. He then spent two years as Chief of the Section of Clinical Science in the National Institute of Alcohol Abuse and Alcoholism in NIH, Bethesda, USA. He returned to England in 1988 to set up the Psychopharmacology Unit in Bristol University, an interdisciplinary research grouping spanning the departments of Psychiatry and Pharmacology, before moving to Imperial College London in December 2008 where he leads a similar group with a particular focus on brain imaging, especially Positron Emission Topography.

He is currently President of the European Brain Council and Chair of the Independent Scientific Committee on Drugs (ISCD) and has previously been President of the British Neuroscience Association, the British Association of Psychopharmacology and the European College of Neuropsychopharmacology as well as Chair of the UK Advisory Council on the Misuse of Drugs. He is a Fellow of the Royal Colleges of Physicians, of Psychiatrists and of the Academy of Medical Sciences. He is also the UK Director of the European Certificate and Masters in Affective Disorders courses and a member of the International Centre for Science in Drug Policy. He has edited the Journal of Psychopharmacology for over twenty years and acts as the psychiatry drugs advisor to the British National Formulary. He has published over 450 original research papers, a similar number of reviews and books chapters, eight government reports on drugs and 28 books, including one for the general public, 'Drugs Without the Hot Air', which won the Transmission book prize in 2014 for Communication of Ideas.

He broadcasts widely to the general public both on radio and television; highlights include being a subject for The Life Scientific on BBC radio 4, several BBC Horizon programs and the Channel 4 documentary Ecstasy-live. He is much in demand for public affairs programs on therapeutic as well as illicit drugs, their harms and their classification. He also lecturers widely to the public as well as to the scientific and medical communities, e.g. at the Cheltenham Science and Hay Literary Festivals, Café Scientifiques and Skeptics in the Pub. In 2010 The Times Eureka science magazine voted him one of the 100 most important

figures in British Science, and the only psychiatrist in the list. In 2013 he was awarded the Nature/Sense about Science John Maddox prize for Standing up for Science

Willem Scholten is a Consultant - Medicines and Controlled Substances. His specialties are pharmaceutical regulatory affairs and drug control policies, with a special interest in realizing access to adequate pain management and for the treatment of opioid dependence for those 5 billion people who have no access.

He studied pharmacy at Utrecht University, Utrecht, the Netherlands, where he obtained a master's in pharmacy and a pharmacist degree (1981). He obtained a master's degree in public administration at the Open University, Heerlen, the Netherlands (2000).

He worked for 10 years in retail pharmacy (1981 - 1991) and for 21 years in public administration. In the Ministry of Health, Welfare and Sport, the Netherlands, he worked on cost containment; legislation; and production and distribution of controlled medicines (1991 – 2005). In the World Health Organization, he was responsible for substance evaluation and access to controlled medicines and he was the Secretary of the Expert Committee on Drug Dependence (2005 - 2012).

At the request of the then Minister of Health, he prepared a major revision of the Opium Act (the Dutch act implementing the international drug control conventions) introducing the obligation for the government to make medical cannabis available to patients. Then, he established the Office of Medicinal Cannabis within the Ministry of Health, Welfare and Sport. As the Head of this Office, he set up the standardized production of medical cannabis including pharmaceutical quality requirements, quality assurance and distribution.

He published over 75 scientific publications, including a number of WHO Guidelines and other WHO documents that were prepared under his leadership.

Philip Wiffen studied pharmacy at the London School of Pharmacy and his career has largely been developed in large teaching hospitals. With extensive experience in clinical pharmacy, Phil has been involved in evidence based medicine for the last 20 years. He established the Cochrane review group for Pain, Palliative and Supportive Care. His particular interest is in systematic reviews of chronic pain and cancer pain. He has authored over 220 peer reviewed publications including many systematic reviews.

Phil is visiting professor in the department of pharmacy and pharmacology at the University of Bath in the UK and developed evidence based practice modules. He has published a book titled 'Evidence based pharmacy' and is lead author on the Oxford Handbook of clinical pharmacy which is now in its 3rd edition.

Phil worked in Indonesia in the late 1970s and several trips to Bangladesh in the 1980s.

He teaches evidence based medicine methodology regularly in China. In the past he has been involved with the WHO work on essential medicines. He has also contributed to WHO guidelines on cancer pain and persistent pain in children. These projects involved developing search strategies, identifying relevant academic papers, appraising the evidence and presenting results using GRADE methods.

About this report

The World Health Organization's (WHO) Expert Committee on Drug Dependence will convene again in November 2016. In spite that the Expert Committee has decided several times to conduct a review of cannabis in "a future meeting", the WHO Secretariat has not been able to prepare the "Pre-review Report", which is an essential requirement for a proper discussion by the ECDD.

DrugScience specially prepared the Pre-review Report "Cannabis and Cannabis Resin" for the Expert Committee's use. This will enable the WHO Expert Committee on Drug Dependence (ECDD) to conduct its first-ever review of the drug. This will rectify the fact that a scientific review of the status of cannabis in the international drug treaties has not been conducted since 1935. If the ECDD conducts a review in its November 2016 meeting, the world-wide prohibition of cannabis can be discussed in the UN's Commission on Narcotic Drugs in March 2018.

DrugScience has requested the WHO to circulate the DrugScience Preview Report in good time among the participants of the 38th Meeting of the ECDD and moreover, also requested that the agenda item of Pre-review of Cannabis and Cannabis Resin be placed on the ECDD Agenda.

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