WHO Expert Committee on Drug Dependence Pre-Review

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Delta-9-tetrahydrocannabinol

Section 5: Epidemiology

World Health Organization

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

Acknowledgments

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a preliminary review for the 40th Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge the contributions of the following individuals who authored this report:

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Contents

1. Industrial use

In our rapid systematic review of the peer-reviewed literature, there were no studies that focused on the industrial use of pure THC other than for therapeutic use (see Appendices 1 and 2, in particular Figure A2). At this point, at least based on a systematic review of the peer-reviewed literature, industrial use seems to be limited to therapeutic use.

In the following, we will only report on applications of pure THC (e.g. dronabinol; (4)); the therapeutic use of THC in combination with other substances (e.g., cannabidiol (5, 6) is described in Report 2 (7)).

To give some examples of therapeutic use from the systematic search: as an analgesic, 10 mg of THC has been found comparable to 60 mg of codeine, and doses of 3.5–10 mg/day of synthetic THC have been found to be effective in multiple sclerosis patients (8). Two trials investigating the use of pure THC for pain associated with multiple sclerosis (9) or fibromyalgia (10) found some evidence of symptom relief, suggesting doses higher than 10 mg/day; however, one study found significant pain reductions to be limited to immediately after THC administration (9) and the other study noted that 5 of 9 patients withdrew due to the adverse event of sedation (10). Three studies on appetite stimulation in patients with cancer or HIV, using doses of THC ranging from 5-7.5 mg/day or 0.1-0.2mg/kg, found some improvement (11) while one trial found no difference in appetite for cancer patients taking either pure THC, THC and cannabidiol, or placebo (12). A survey on therapeutic cannabis use in a study in Germany reported average THC doses of 14.9 mg/day (range: 4-35 mg/day; N=14); symptoms being treated included neurological, gastrointestinal and pain (13).

In regard to the clinical use of pure THC, liquid dronabinol is typically marketed in a 5 mg/mL form (14) or in capsules of 2.5, 5 or 10 mg (15). One trial in cancer patients with cachexia found bi-daily dosing of 2.5 mg dronabinol to be more effective for both increasing appetite and decreasing weight loss as compared to either 2.5 mg/day or 5 mg/day (14). A review on the use of THC for cancer-related cachexia indicated that individual titration may be more effective than fixed dosing (16) and this has been suggested for HIV wasting syndrome as well (15). Doses of 5 mg and 10 mg dronabinol were associated with increased caloric intake in regular marijuana users with HIV; however, tolerance to dronabinol is a concern when treating marijuana users (14).

2. Non-medical use, abuse and dependence

Tinctures and extracts of cannabis for medical reasons date to Chinese applications documented 4000-5000 years ago (8, 17). In Europe and North America, use was introduced in the 19th century. Pure THC preparations are more recent and dronabinol (synthetic pure THC) was approved in 1985 in the US.

While pure THC has potential for non-medical use and abuse, such non-medical use seems to be rare (4, 18). A small trial reported no results to date (https://clinicaltrials.gov/ct2/show/NCT02094599).

3. Nature and magnitude of public health problems related to misuse, abuse and dependence

No reports were found of public health problems of pure THC.

4. Licit production, consumption, international trade

The results of our systematic review did not yield any articles related to licit production, consumptions, or international trade of pure THC.

5. Illicit manufacture and traffic

No indication of illicit manufacture or traffic was found in the peer-reviewed literature.

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Appendix 1: Original Search Strategy for peer-reviewed articles on Delta-9-tetrahydrocannabinol

The following systematic searches of the peer-reviewed literature were conducted originally based on the PRISMA guidelines (19, 20) and using three databases via OVID on March 8, 2018:

1. Embase
2. Medline
3. PsycINFO

The search was restricted to literature published in 2000 and onwards. Various search strategies were explored by the authors independently using different combinations of keywords and MeSH terms pertinent to epidemiology, cannabis-related compounds, substance abuse, self-medication and therapeutic use. This was done to determine an optimal unanimous search strategy for each report, to identify the most relevant studies, respecting the short timeframe available to prepare this Pre-Review.

As a result, Report 3 (on Delta-9-tetrahydrocannabinol) and 4 (Isomers of THC) shared the same search parameters due to a low search count for isomers of THC, which was a subset of the results obtained from the searches for Report 3. Results from the searches were screened in parallel by different authors of this report (HF, VT, OSMH, JR), and any studies relevant to a parallel report were exchanged between the authors during the review.

Table A1: Original search strategy for Report 3

No.	Searches	Results
1	Human/ or humans/	36244807
2	limit 1 to yr="2000 -Current"	21066974
3	(bibliography or case reports or clinical conference or conference abstract or conference paper or conference proceeding or "conference review" or comment or editorial or in vitro or letter).pt.	8530671
4	2 not 3	16300231
5	epidemiology or exp epidemiology/	3693795
6	prevalence or exp prevalence/	1580556
7	incidence or exp incidence/	1888341
8	population or exp population/	3537733
9	5 or 6 or 7 or 8	8094152
10	delta-9-tetrahydrocannabinol	6047

11	tetrahydrocannabinol or thc	25380
12	dronabinol or exp dronabinol/	13589
13	10 or 11 or 12	29610
14	4 and 9 and 13	1331
15	remove duplicates from 14	1055

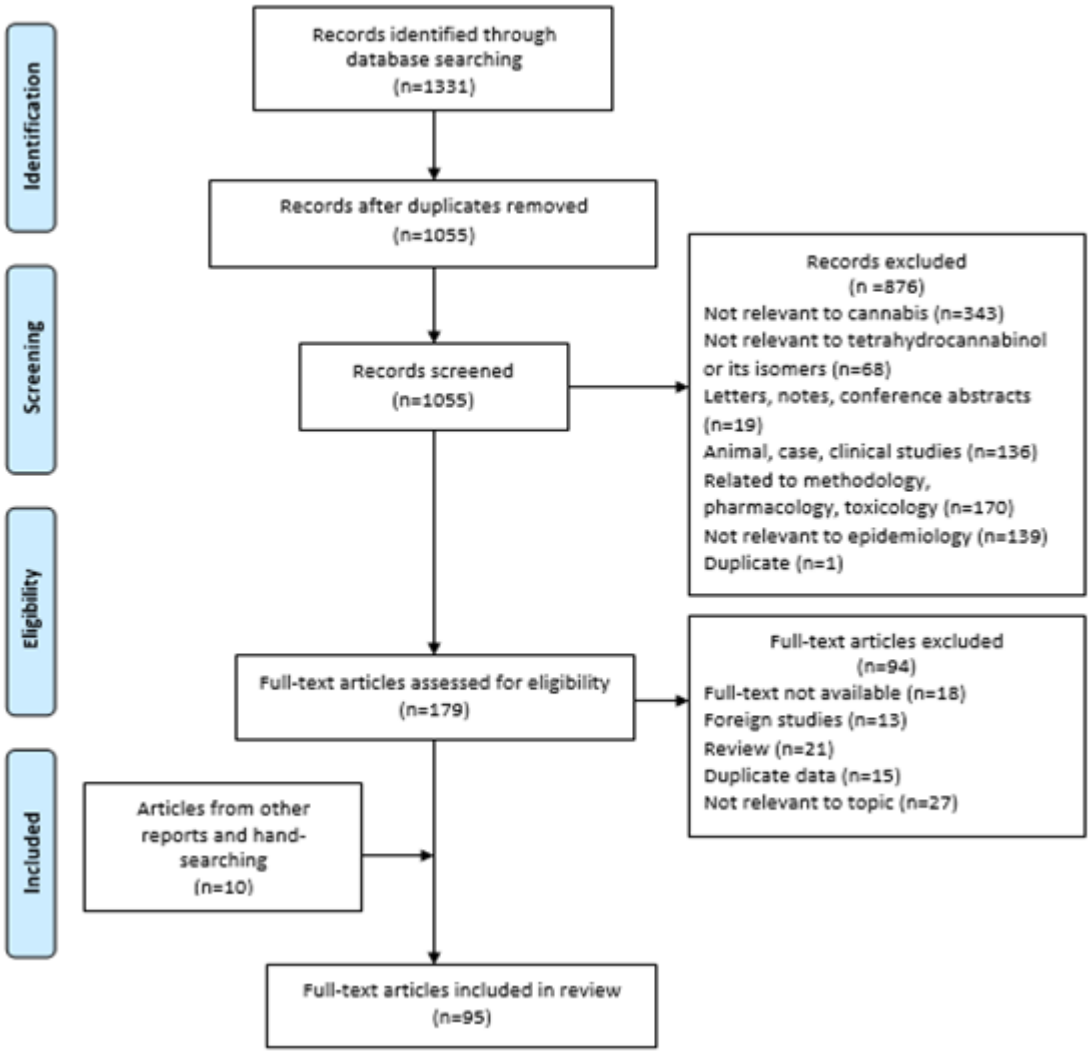
A full list of references can be found in a separate Reference Appendix document.

Reviewing the studies for inclusion was a two-step screening process:

1. Based on title and abstract screening, studies with minimal uncertainty were excluded.
2. Based on full-text review of studies remaining at step 1, studies were selected for final inclusion and data was abstracted at this point.

Each step of the review was led by a pilot screening of 20 studies to maintain consistency between the authors taking part in the review. In addition, coding of studies was compared systematically for 20 studies between VT, HF, OSMH and JR. The authors also met on a weekly basis throughout the duration of the review to discuss the progress of the reports and to resolve any conflicts during study selection and coding. The results of the searches are summarized in Figure 3.

Figure A1: PRISMA Diagram for Report 3 (21)



Of 1055 studies retrieved from the search, 179 were included after screening of title and abstract (see Appendix 1 for Reports 3 for details). After full-text screening, 95 studies were included in report 1. Review articles were excluded from analysis but were kept for the background of the report and inserted into the various chapters.

However, no articles were found on pure THC. This has led to a revised search strategy (see Appendix 2).

Appendix 2: Revised search Strategy for peer-reviewed articles on Delta-9-tetrahydrocannabinol

Please find below the revised strategy for searches on pure THC. The searches were carried out in the same databases on Monday April 30, 2018, after exploring several other options the days before.

Table A2: Revised search strategy for Report 3

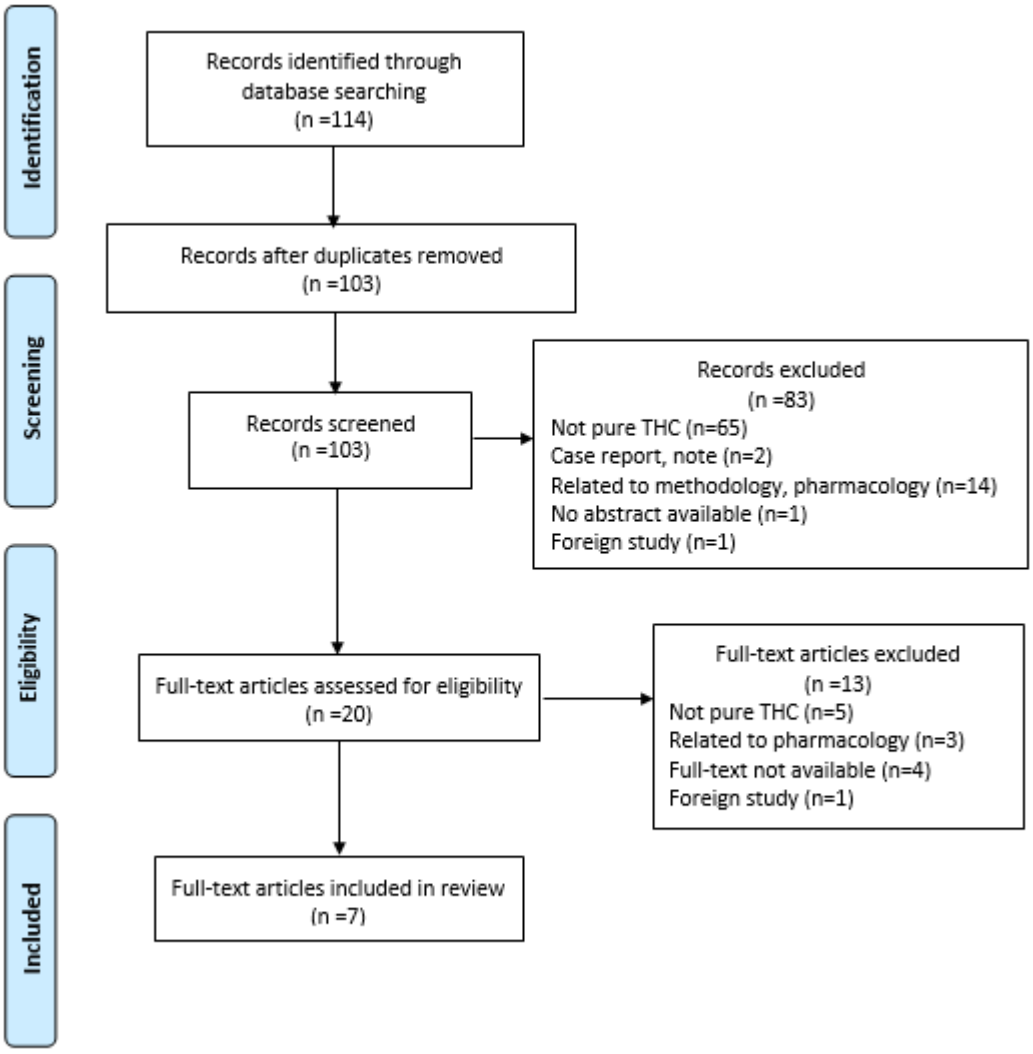
	Searches	Results
1	Human/ or humans/	36624572
2	limit 1 to yr="2000 -Current"	21436269
3	(bibliography or case reports or clinical conference or conference abstract or conference paper or conference proceeding or "conference review" or comment or editorial or in vitro or letter or clinical trial).pt.	8678776
4	2 not 3	16557485
5	*Dronabinol/	7689
6	pure thc	33
7	pure delta-9-tetrahydrocannabinol	6
8	5 or 6 or 7	7708
9	epidemiology.mp. or exp epidemiology/	3754882
10	prevalence.mp. or exp prevalence/	1606016
11	population.mp. or exp population/	3590357
12	9 or 10 or 11	7186552
13	4 and 8 and 12	114
14	remove duplicates from 13	103

Note on terminology and search strategy

With regard to chapter headings, we used the headings as specified in the WHO Request for Proposals. In the text, we did not use terms like misuse or abuse, which are not or not consistently defined within the current medical classification systems (1, 2), and thus we only use the terms cannabis use, cannabis use disorders and cannabis dependence. All terms are defined in the text, based on the above cited current medical classification systems.

The literature searches were not restricted to the above-mentioned medical terminology. They were restricted to pure Delta-9-tetrahydrocannabinol (THC). If articles were reporting THC in general (e.g. as indication of cannabis use in a region by measuring THC in wastewater), the findings were included in Report 1 (3).

Figure A2: Revised PRISMA Diagram for Report 3



All full-text articles assessed for eligibility can be found on a separate Appendix file.

Appendix 3: Abbreviations

BCO : Butane Cannabis Oil
CI: 95% Confidence interval
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
DSM-5: Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
DUI: Driving Under the Influence
EMCDDA: European Monitoring Centre for Drugs and Drug Addiction
ESPAD: European School Survey Project on Alcohol and Other Drugs
EU: European Union
GBD: Global Burden of Disease
ICD-10: International Classification of Diseases – 10th Revision
INCB: International Narcotics Control Board
IUPAC: International Union of Pure and Applied Chemistry
MC: Medical cannabis (abbreviated only in the respective chapter)
UNODC: United Nations Office on Drugs and Crime
THC: Tetrahydrocannabinol (Δ9-tetrahydrocannabinol)
WDR: World Drug Report
WHO: World Health Organization