

WHO Expert Committee on Drug Dependence Pre-Review

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Extracts and tinctures of cannabis

Section 5: Epidemiology



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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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1. Industrial use

In our rapid systematic review of the peer-reviewed literature, there were no studies that focused on the industrial use of cannabis tinctures and extracts. At this point, industrial use seems to be limited to therapeutic use.

Tinctures, often sublingual, and sprays are routes of administration for medical cannabis. Typically, tinctures are mixed with ethanol, but vinegars and glycerin may also be used. The sublingual extracts are dropped under the tongue and held for a period of time sufficient to permit absorption by the branches of the lingual artery, including the sublingual and deep lingual arteries. If used properly, onset of action and bioavailability may be faster and higher for this route compared with oral administration, as is often observed with other drugs. Tinctures may be a favorable option in the future, as they mitigate the dosing and bioavailability issues associated with orally ingested cannabis and eliminate issues of tolerability with inhaled cannabis (3).

Overall, the use of tinctures is not widespread today, and evidence supporting the therapeutic use of tinctures is limited.

Nabiximols is used therapeutically as an oromucosal spray, contains 27 mg THC and 25 mg cannabidiol per ml. The medication is licensed for use in the United Kingdom, Spain, Czech Republic, Germany, Denmark, Sweden, Italy, Austria, Canada, Poland, France (for spasticity due to multiple sclerosis), but currently not in the United States (initial target indication for US FDA approval is cancer pain). The pharmaceutical is used for spasticity, pain, nausea and vomiting, and, to date, more than 19 trials have been conducted (4).

There are a number of other tinctures and oils containing cannabidiol, which are currently being used under medical cannabis legislations or illegally, but unsanctioned (5). Some of these have been included in randomized controlled trial (4).

2. Non-medical use, abuse and dependence

2.1 Background

Tinctures and extracts of cannabis for medical reasons date to Chinese applications documented 4000-5000 years ago (3, 6). In Europe and North America, use was introduced in the 19th century. However, in part due to the current status, cannabis medications are relatively rare, and this includes extracts and tinctures. There is a clear link between the medical availability of psychoactive drugs and its non-medical use. Thus, if cannabis extracts and tinctures are only rarely used medically, non-medical use is also expected to be rare.

For non-medical use, the cannabis extracts and tinctures are usually consumed in the form of oil or as wax, which is also called butane cannabis oil (derived from the process required to make it; BCO). Smoking BCO is also called dabbing, but cannabis extracts can be vaporized, eaten and drunk as well.

2.2 Epidemiology of use of cannabis extracts and tinctures

There were three prevalence studies found in the literature specifically related to tinctures and extracts use (7-9). One of the studies reported global data from an ad-hoc internet sample of drug users, whereas the others were based on high-school and university students from the United States. Obviously, these studies can only give a very selective view on the prevalence of tinctures and abstracts.

The global study (8) was based on the Global Drug Survey, an online-survey answered by 181,870 drug users from over 50 countries in 2015 and 2016. In this study, 46% of respondents were past-year cannabis users, out of which 7% reported using BCO. The proportion of users of cannabis oil amongst cannabis users might be an overestimate and should be treated with caution (8), as we have no indication what population this arbitrary sample represents.

In this Global Drug Survey, motives for cannabis use (i.e., recreational vs. medicinal) of 5,922 BCO users were assessed (8). Among the surveyed BCO users, 1.2% considered their cannabis use to be exclusively medical, while the majority specified both recreational and medical use motives (57.1%), and exclusively recreational use was reported by four out of ten respondents (41.7%). Compared to non-BCO users, BCO users appeared to be more prone to medicinal cannabis use and also to source their cannabis through prescriptions or their own cultivation. As indicated above, it is not clear to which population these results can be generalized (8).

In an anonymous survey conducted in Connecticut (US) in 2014 (7), application of wax and cannabis oil in e-cigarettes was studied in a sample of high-school students. Among lifetime cannabis users (N=1,123), experience with vaporization of cannabis oil and wax was found at 15.5% and 10.2%, respectively. These rates were higher for those with lifetime experience of e-cigarettes (cannabis oil: 22.9%, wax: 14.8%) (7).

In another cross-sectional study of 821 university students in a U.S. state where medical cannabis use is legal but recreational use is not, respondents completed an online survey about their health and health behavior as part of course credit or extra credit. Participants who had used cannabis in the past year (33%, n=273) completed questions about their use of BCO and cannabis-related problems. Among past-year cannabis users, 44% (n=121) had used BCO in the past year. More frequent BCO use was associated with higher levels of physical dependence, even after accounting for potential confounders (9).

2.3 Links to cannabis use disorders dependence

Except for the already reported study in US university students (9), which found that frequency of BCO use was associated with higher levels of physical dependence, no other study was found. This study corroborates the evidence in Report 1 on the association between levels of THC potency and risk of dependence (10).

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

In our rapid systematic review, there were three studies that focused on the nature and magnitude of the public health problem related to the use of cannabis tinctures and extracts (11). In a study by Romanowski that looked at legalization of cannabis in four states, charts of patients who presented to the burn center with suspicion of BCO-related injuries between January 2007 and December 2014 were examined. Results showed that there was an increase in burn injuries related to the production of BCO. Three patients died as a result of their injuries. Patients required a mean of 12+/-48.4 ventilator days, and 27.1+/-59.4 days in the hospital. Results showed that there has been a steep rise in the number of patients presenting with burn-associated BCO production in the region over the past 7 years. These burn injuries are a public health concern in the United States (11-13).

In another cross-sectional study from Colorado, United States, researchers utilized the National Burn Repository to capture all hydrocarbon burns reported to the local burn center from January 1st, 2008, through August 31st, 2014. Results showed that twenty-nine cases of BCO burns were admitted to the local burn center during the study period. Zero cases presented prior to medical liberalization, 19 (61.3%) during liberalization of medical use (October 2009-December 2013), and 12 (38.7%) in 2014 since legalization. Nineteen patients required skin grafting, eight received wound care only, one required surgical fracture repair, and one required surgical debridement. Since the legalization of cannabis in Colorado, hydrocarbon burns associated with cannabis oil production have increased (12).

In a study by Loflin et al., researchers gathered preliminary information on BCO users and tested whether BCO use was associated with more medical problems than using herbal cannabis. In a sample of 357 participants, the study did not find higher rates of accidents or burns among BCO users (13).

4. Licit production, consumption, international trade

The results of our systematic review did not yield any articles related to licit production, consumptions, and international trade of cannabis extracts and tinctures.

5. Illicit manufacture and traffic

As indicated above, the UN monitoring system, mainly UNODC, annually updates on illicit production and trade. According to the last World Drug Report, seizures of tinctures played comparatively a negligible role in 2015 (14).

Appendix 1: Search Strategy for Extracts and Tinctures of Cannabis

The same general procedure was used for searching (albeit with different keywords – see below), processing and quality control for extracts and tincture of cannabis as employed in Report 1.(10) Table A1 shows the results.

Table A1: Search Strategy for extracts and tinctures of cannabis

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	cannabis or exp cannabis/	71067
11	marijuana or exp marijuana/	68545
12	10 or 11	89320
13	12 and extract	1540
14	12 and tincture	30
15	12 and oil	712
16	12 and aqueous	148
17	Nabiximols	742
18	13 or 14 or 15 or 16 or 17	2923
19	4 and 9 and 18	233
20	Dependence	588264
21	Abuse	549267
22	Disorder	2664499

23	self-medication	19180
24	Therapeutic	2333110
25	20 or 21 or 22 or 23 or 24	5766886
26	4 and 18 and 25	567
27	19 or 26	681
28	remove duplicates from 27	587

We followed the final epidemiology terms of reference for the formal inclusion and exclusion criteria and added additional relevant inclusion/ exclusion criteria that were pertinent to the focus of our report on the epidemiology of cannabis extracts and tinctures. The formal inclusion and exclusion criteria are found in Appendix 2.

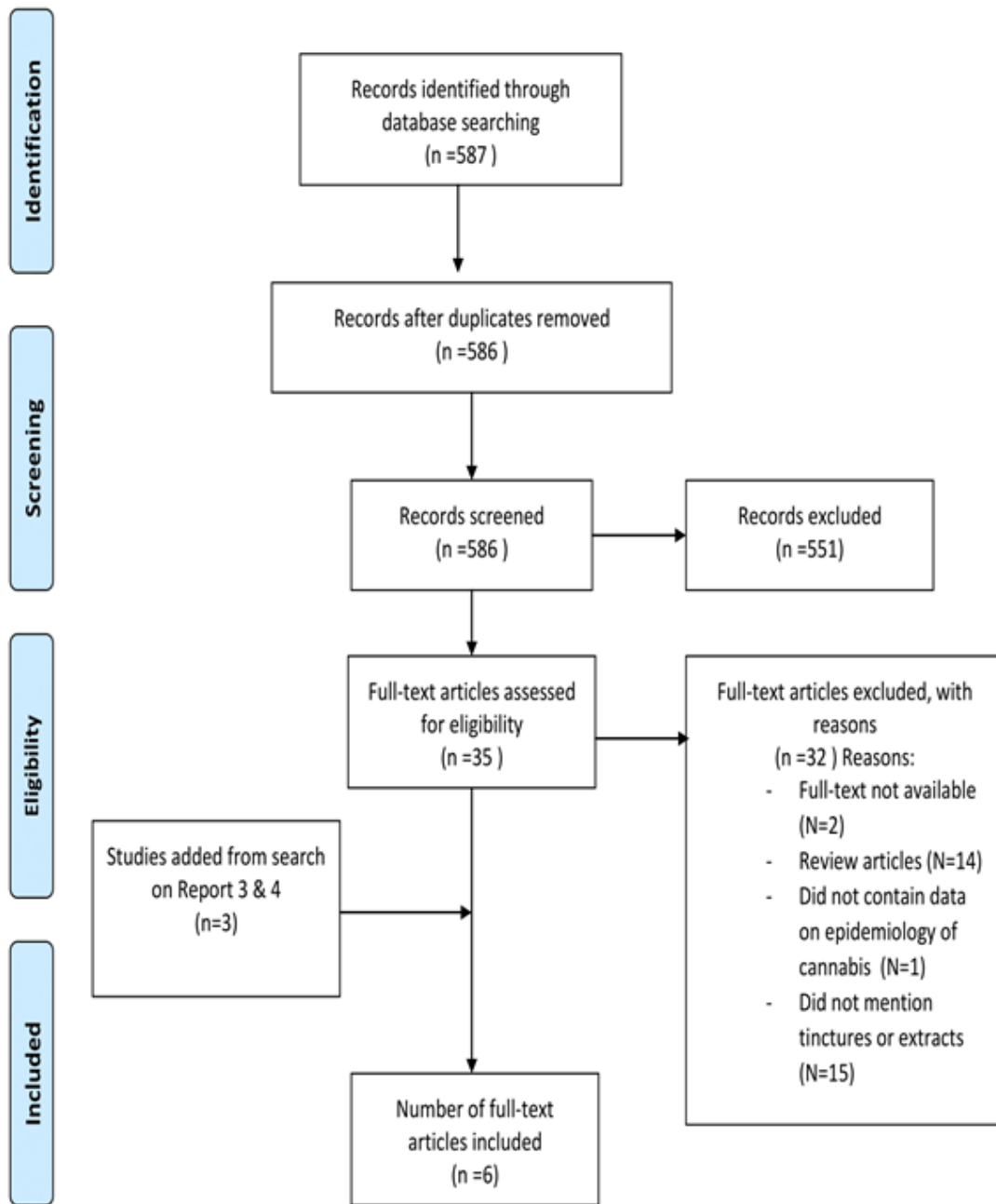
Of 587 studies retrieved from the search, N=35 were included for full-text eligibility after title and abstract screen, of which 32 were excluded for the following reasons: full-text not available (N=2), review articles (N=14), did not contain data on epidemiology of cannabis (N=1), did not mention tinctures or extracts (N=15). After full-text screening and adding N=3 articles from the original search for Report 3 & 4, 6 full-text articles were included in this report. Review articles were excluded at the full-text screening stage from analysis but were kept for the background of the report. In Figure A1, a flow diagram shows each of the identification, screening, eligibility, and inclusion phases of the systematic review.

Note on terminology

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.

Figure 1: PRISMA diagram for Report 2



Template for the flow chart: (15)

Appendix 2: Report 2 Inclusion and Exclusion Criteria

For Report 2, the formal inclusion and exclusion criteria were:

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of *Cannabis sativa*
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of *Cannabis sativa*.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. cannabis tea
- Nabiximols (e.g. Sativex®)
- Reviews on cannabis that include the epidemiology
- Any clinical conditions for which cannabis was used medically or for therapeutic use (also being admitted to a psychiatric facility for cannabis use)
- Driving under the influence of cannabis
- Self-medication and the epi of self-medication is reported

Exclusion criteria

Studies to be excluded from the report involve:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
 - Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant. (-)-trans-delta-9-tetrahydrocannabinol
 - (+)-trans-delta-9-tetrahydrocannabinol
 - (-)-cis-delta-9-tetrahydrocannabinol
 - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
 - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
 - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (6aR,10aR)- 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol
- Articles focusing solely on therapeutic use without epidemiology of cannabis extracts or tinctures
- Methodological development papers or conference abstracts

- Abstract and full-text was not available
- In vivo or animal studies
- Randomized Control Trials
- Small populations such as club patrons, ship sailors, etc.
- Sexual assault and violent offenders
- <100 sample size

Appendix 3: Abbreviations

BCO :	Butane Cannabis Oil
CI:	95% Confidence interval
DSM-IV:	Diagnostic and Statistical Manual of Mental Disorders – 4 th Edition
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders – 5 th 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 – 10 th 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 (Δ^9 -tetrahydrocannabinol)
WDR:	World Drug Report
WHO:	World Health Organization

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