WHO Expert Committee on Drug Dependence

Critical Review

....

Delta-9-tetrahydrocannabinol

World Health Organization

Acknowledgments

Delta-9-tetrahydrocannibinol

Section 1: Chemistry

Contents

Section 1: Chemistry

1. Substance identification

Delta-9-tetrahydrocannabinol refers to the four stereoisomers:[1]

a. (−)-*trans*-delta-9-tetrahydrocannabinol (also known as dronabinol)[2]

b. (+)-*trans*-delta-9-tetrahydrocannabinol

c. (−)-*cis*-delta-9-tetrahydrocannabinol

d. (+)-*cis*-delta-9-tetrahydrocannabinol

1.1 International Nonproprietary Name (INN)

Dronabinol[2]

1.2 Chemical Abstract Service (CAS) Registry Number

- (−)-*trans*-delta-9-tetrahydrocannabinol (dronabinol): 1972-08-3
- (+)-*trans*-delta-9-tetrahydrocannabinol: 17766-02-8
- (−)-*cis*-delta-9-tetrahydrocannabinol: 43009-38-7
- (+)-*cis*-delta-9-tetrahydrocannabinol: 69855-10-3

1.3 Other Chemical Names[3]

1.3.1 delta-9-tetrahydrocannabinol:

- 6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol[4(A)]

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[1] Delta-9-tetrahydrocannabinol chemically comprises the four stereoisomers listed, as described in the report of "dronabinol" of the 34th meeting of the ECDD (34thECDD_dronabinol).

[2] Dronabinol refers to primary psychoactive compound in botanical cannabis (*Cannabis sativa* L.) (−)-*trans*-delta-9-tetrahydrocannabinol.

[3] Reported by Chemical Abstract Service (CAS).

[4] Alternate numbering systems: (A)"Dybenzopyran"; (B) "Monoterpenoid"

Section 1: Chemistry

1.3.2 (–)-trans-delta-9-tetrahydrocannabinol (dronabinol):

- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR-trans*)- [4(A)]

- Cannabinol, tetrahydro- (6CI)

- (6*aR*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]

- (–)-*trans*-Δ^9-THC [4(A)]

- (–)-*trans*-Δ^9-Tetrahydrocannabino[4(A)]

- (–)-Δ^9-Tetrahydrocannabinol [4(A)]

- (–)-Δ^9-*trans*-Tetrahydrocannabinol [4(A)]

- (6*aR*,10*aR*)-6,6,9-trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol [4(A)]

- Abbott 40566

- Cannabinoids, THC

- Dronabinol

- Marinol

- NSC 134454

- Namisol

- QCD 84924

- SP 104

- THC

- Tetrahydrocannabinol

- *trans*-(–)-Δ^9-Tetrahydrocannabinol [4(A)]

(A)
Delta-9-THC   =   (B)
Delta-1-THC

5
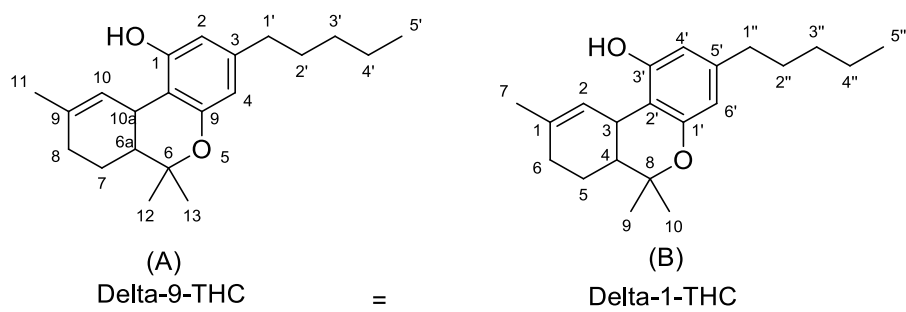
- *trans*-Δ^9-Tetrahydrocannabinol [4(A)]
- Δ^9-THC [4(A)]
- Δ^9-Tetrahydrocannabinol [4(A)]
- Δ^9-*trans*-Tetrahydrocannabinol [4(A)]
- Cannabinol, Δ^1-tetrahydro- (7CI) [4(B)]
- (−)-3,4-*trans*-Δ^1-Tetrahydrocannabinol [4(B)]
- (−)-*trans*-Δ^1-Tetrahydrocannabinol [4(B)]
- (−)-Δ^1-Tetrahydrocannabinol [4(B)]
- (l)-Δ^1-Tetrahydrocannabinol [4(B)]
- l-*trans*-Δ^9-Tetrahydrocannabinol [4(B)]
- l-Δ^1-*trans*-Tetrahydrocannabinol [4(B)]
- Δ^1-THC [4(B)]
- Δ^1-Tetrahydrocannabinol [4(B)]

1.3.3   (+)-trans-delta-9-tetrahydrocannabinol:

- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (+)- (8CI) [4(A)]
- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-*trans*)- [4(A)]
- (6*aS*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]
- (+)-*trans*-Δ^9-Tetrahydrocannabinol [4(A)]
- (+)-Δ^1-Tetrahydrocannabinol [4(B)]
- (+)-Δ^9-THC [4(A)]
- (+)-Δ^9-Tetrahydrocannabinol [4(A)]
- *d*-Δ^9-Tetrahydrocannabinol [4(A)]
- *trans*-(+)-Δ^9-Tetrahydrocannabinol [4(A)]

1.3.4   (−)-cis-delta-9-tetrahydrocannabinol:

- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-*cis*)- [4(A)]
- (6*aS*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]
- *cis*-Δ^9-Tetrahydrocannabinol [4(A)]

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1.3.5   (+)-cis-delta-9-tetrahydrocannabinol:

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-cis)- [4(A)]
- (6aR,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol [4(A)]

1.4   Trade names [1]

1.4.1   (−)-trans-delta-9-tetrahydrocannabinol (dronabinol or (−)-trans-Δ^9-THC):

Canada: **Marinol** (preparation discontinued or no longer actively marketed);

Israel: **Ronabin** (preparation discontinued or no longer actively marketed);

South Africa: **Elevat** (preparation discontinued or no longer actively marketed);

United States: **Marinol**[1]; **Syndros**[2];

United States Pharmacopeia USP 40: **Dronabinol Capsules**[3]

- (+)-*trans*-delta-9-tetrahydrocannabinol ((+)-*trans*-Δ^9-THC): N/A

- (−)-*cis*-delta-9-tetrahydrocannabinol ((−)-*cis*-Δ^9-THC): N/A

- (+)-*cis*-delta-9-tetrahydrocannabinol ((+)-*cis*-Δ^9-THC): N/A

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[1] MARINOL is supplied as round, soft gelatin capsules for oral use as follows: • 2.5 mg white capsules • 5 mg dark brown capsules • 10 mg orange capsules. Each MARINOL capsule strength is formulated with the following inactive ingredients: 2.5 mg capsule contains gelatin, glycerin, sesame oil, and titanium dioxide; 5 mg capsule contains iron oxide red and iron oxide black, gelatin, glycerin, sesame oil, and titanium dioxide; 10 mg capsule contains iron oxide red and iron oxide yellow, gelatin, glycerin, sesame oil, and titanium dioxide

[2] SYNDROS (dronabinol) oral solution, 5 mg/mL is a clear, pale yellow to brown solution. Each milliliter of SYNDROS contains 5 mg of dronabinol as an active ingredient and the following inactive ingredients: 50 % (w/w) dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole, and water.

[3] Dronabinol in sesame oil.

Section 1: Chemistry

1.5 Street Names

N/A

1.6 Physical Appearance

1.6.1 (−)-trans-delta-9-tetrahydrocannabinol (or (−)-trans-Δ^9-THC):

Colourless to light yellow resinous oil at room temperature, which tends to solidify at lower temperature [2-6]

1.6.2 (+)-trans-delta-9-tetrahydrocannabinol (or (+)-trans-Δ^9-THC):

Colorless oil [5]

1.6.3 (−)-cis-delta-9-tetrahydrocannabinol (or (−)-cis-Δ^9-THC):

Colorless oil [5]

1.6.4 (+)-cis-delta-9-tetrahydrocannabinol (or (+)-cis-Δ^9-THC):

Colorless oil [5]

1.7 WHO Review History

• Delta-9-Tetrahydrocannabinol (Delta-9-THC) and its stereo-chemical variants with one variant being dronabinol ((-)-trans-delta-9-THC), are currently listed in Schedule II of the 1971 Convention on Psychotropic Substances. Delta-9-THC was originally included in Schedule I of the 1971 Convention at the time of its adoption, together with its stereo-chemical variants.

• In 1989, the WHO ECDD recommended, based on the critical review of Dronabinol ((-)-trans-delta-9-THC) undertaken at its 26th meeting in 1988, that Dronabinol be moved to Schedule II while keeping the other isomers and stereo-chemical variants in Schedule I. WHOs proposal to transfer dronabinol to Schedule II was rejected by the CND at its 11th special session in 1990.

• At its 27th meeting in 1990, the ECDD carried out a critical review of updated information on Delta-9-THC. It recommended that Delta-9-THC and all its isomers and stereo-chemical variants be rescheduled from Schedule I to Schedule II of the 1971 Convention. This was done in order to avoid a distinction between Delta-9-THC and stereo-chemical variants, their placement under different schedules and

prevent potential legal and forensic analytical problems. This recommendation was adopted by the CND at its 34th session in 1991.

• At its 33rd ECDD meeting in 2002, Delta-9-THC was again critically reviewed. The Committee recommended that dronabinol and its stereo-chemical variants be rescheduled from Schedule II to Schedule IV of the 1971 Convention. However, no further procedural steps were taken, i.e. there was no formal communication of this recommendation from WHO to the CND.

• At its 34th meeting in 2006, the ECDD carried out an assessment of an updated dronabinol critical review report. The Committee concluded that although dronabinol constitutes a substantial risk to public health, this risk is different from those related to cannabis— controlled under the 1961 Convention. The substance was found to have moderate therapeutic usefulness, with a likelihood of an increase in its medical use because of continuing clinical research. Therefore, the Committee recommended that dronabinol and its stereo-chemical variants be rescheduled from Schedule II to Schedule III of the 1971 Convention.

• In March 2007, at its 50th session, the CND decided by consensus not to vote on the recommendation of the WHO to transfer dronabinol and its stereo-chemical variants from Schedule II to Schedule III of the 1971 Convention. Furthermore, the CND requested the WHO, in consultation with the INCB, as appropriate, to undertake, for consideration by the Commission, a review of dronabinol and its stereo-chemical variants when additional information became available (CND Decision 50/2).

• At its 35th meeting in 2012, the ECDD discussed the CND's recommendations of 2007. The Committee did not carry out a review of dronabinol, but reinstated the recommendation made by the 34th ECDD to move dronabinol and its stereo-chemical variants from Schedule II to Schedule III of the 1971 Convention. The ECDD decided that the previous ECDD decision on dronabinol and its stereo-chemical variants should stand, since it was unaware of any new evidence that was likely to materially alter the scheduling recommendation made at its 34th meeting. This recommendation was communicated by the Director-General of the WHO to the Secretary-General in October 2012.

• The CND reconsidered this issue in March 2013 at its 56th session. Concern was expressed by several delegations that, despite the recommendation received from WHO, no decision had yet been taken by the Commission to reschedule dronabinol and its stereo-chemical variants. A number of delegations noted that they were not able to support the recommendation made by WHO regarding dronabinol, as that recommendation could hinder efforts to prevent international cannabis abuse and could send a

confusing message regarding the harm associated with the use of cannabis. It was suggested that WHO should continue reviewing dronabinol.

• In March 2014, based on the recommendation made by the ECDD at its 35th meeting in 2012, CND voted against moving dronabinol and its stereo-chemical variants from Schedule II to Schedule III of the 1971 Convention.

• At its 38th meeting in 2016 the ECDD requested that delta-9-tetrahydrocannabinol (THC) be pre-reviewed along with cannabis and cannabis resin, extracts and tinctures of cannabis, cannabidiol (CBD) and isomers of THC.

• At its 40th meeting in June 2018 the ECDD evaluated the above mentioned pre-reviews and recommended to proceed to the critical reviews of cannabis and cannabis resin, extracts and tinctures of cannabis, delta-9-THC and isomers of THC at the 41st meeting in November 2018.

2. Chemistry

2.1 Chemical Name

2.1.1 IUPAC Name:

    2.1.1.1 (−)-trans-Δ^9-THC:

(6*aR*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

    2.1.1.2 (+)-trans-Δ^9-THC:

(6*aS*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

    2.1.1.3 (−)-cis-Δ^9-THC:

(6*aS*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

    2.1.1.4 (+)-cis-Δ^9-THC:

(6*aR*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

2.1.2 CA Index Name:

    2.1.2.1 (−)-trans-Δ^9-THC:

6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR*,10*aR*)-

    2.1.2.2 (+)-trans-Δ^9-THC:

6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*,10*aS*)-

    2.1.2.3 (−)-cis-Δ^9-THC:

6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*,10*aR*)-

    2.1.2.4 (+)-cis-Δ^9-THC:

6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR*,10*aS*)-

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2.2 Chemical Structure

Free base:
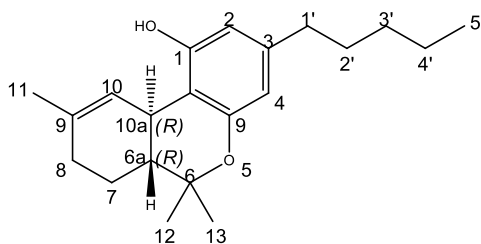
(6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(-)-trans-delta-9-tetrahydrocannabinol
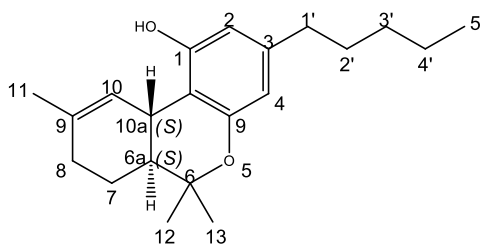
(6aS,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(+)-trans-delta-9-tetrahydrocannabinol
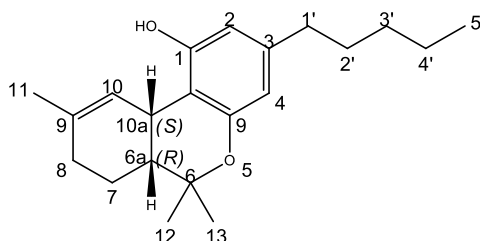
(6aR,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(+)-cis-delta-9-tetrahydrocannabinol
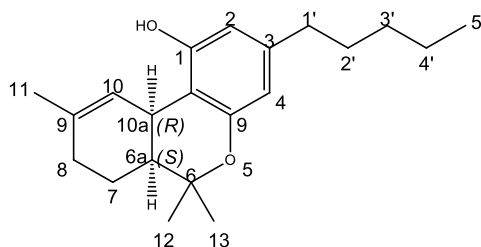
(6aS,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(-)-cis-delta-9-tetrahydrocannabinol

Molecular Formula: $C_{21}H_{30}O_2$

Molecular Weight: 314.46

2.3 Stereoisomers

Δ^9-THC has two chiral carbon atoms C6*a* and C10*a*, which generate four stereoisomers:

(−)-*trans*-Δ^9-THC and (+)-*trans*-Δ^9-THC, (−)-*cis*-Δ^9-THC and (+)-*cis*-Δ^9-THC.

Naturally occurring in cannabis is the (−)-*trans*-Δ^9-THC. The other three stereoisomers have been recently synthetized [5].

2.4 Methods and Ease of Illicit Manufacturing

(−)-*trans*-Δ^9-THC can be obtained mainly by four methods:

1. Natural source: extraction of Δ^9-tetrahydrocannabinolic acid (THCA), decarboxylation and purification
2. Decarboxylation of THCA and purification
3. Semi-synthesis: extraction of cannabidiolic acid (CBDA), decarboxylation and conversion into THC
4. Total synthesis from terpene and olivetol

2.4.1   Natural source

(−)-*trans*-Δ^9-THC does not occur at significant concentration in the living cannabis plant. The plant synthesizes primarily the carboxylic acid form of (−)-*trans*-Δ^9-THC, namely, Δ^9-tetrahydrocannabinolic acid (THCA)[7] from cannabigerolic acid and accumulates in the glandular trichomes of flowers and leaves where it represents up to 90% of the total THC samples [7, 8].

Contrary to (−)-*trans*-Δ^9-THC, THCA does not elicit intoxicating effects in humans [7].[1]

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[1] THCA is not a scheduled substance.

Section 1: Chemistry

This acidic cannabinoid is thermally unstable and can be quickly decarboxylated when exposed to heat via smoking or baking [9].

In order to obtain Δ^9-THC from cannabis plant it is possible to follow two strategies:

- Decarboxylation of cannabis inflorescence prior to extraction
- Extraction and decarboxylation of THCA into (−)-*trans*-Δ^9-THC.

Both processes are described in the literature. As an example, the method of extraction of (−)-*trans*-Δ^9-THC and THCA is reported in the patent US8846409B2 [10].

The extraction of (−)-*trans*-Δ^9-THC involves the heating of cannabis inflorescence, which is preliminarily shredded in 2 mm particles in two phases, the first at 105 °C for 15 minutes and the second at 120 °C for 2 hours in order to decarboxylate at least 95% of THCA. Subsequently, the plant material is extracted with either supercritical carbon dioxide (CO_2) or an organic solvent, such as alcohol or hexane, which is evaporated to obtain a solid residue. The latter is dissolved into hot ethyl alcohol and left at −20 °C for two days in order to precipitate wax and other impurities, which are removed by filtration. The filtrate is dried and (−)-*trans*-Δ^9-THC is separated from the other components by chromatography through a column packed with Sephadex LH20, eluting with 2:1 chloroform/dichloromethane. (−)-*trans*-Δ^9-THC is then purified from methanol and pentane.

2.4.2 Decarboxylation of THCA and purification

THCA is extracted as a crystalline solid following a procedure similar to that employed for neutral (−)-*trans*-Δ^9-THC but without the heating step. If heated up (i.e. smoked or baked), THCA decarboxylates to give neutral (−)-*trans*-Δ^9-THC.[1]

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[1] For forensic analysis the total THC is required, that is the sum of neutral THC and THCA. A gas chromatographic method is generally employed, thus the non-derivatized sample is heated up in the injector and THCA converts into neutral THC. The yield of decarboxylation is strictly dependent from the temperature and geometry of the injector.

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(6aR,10aR)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-2-carboxylic acid
(-)-*trans*-delta-9-tetrahydrocannabinolic acid

(6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(-)-*trans*-delta-9-tetrahydrocannabinol
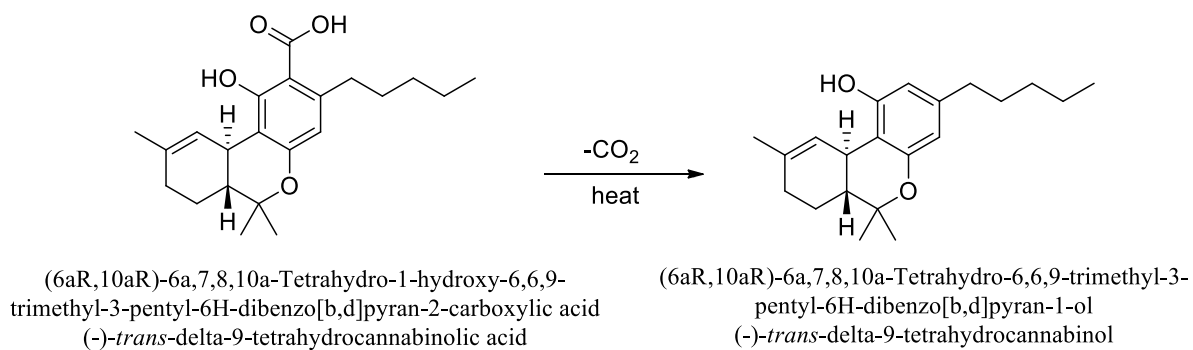
2.4.3   Semi-synthesis

(−)-*trans*-Δ^9-THC can be obtained by partial synthesis from cannabidiol (CBD) [6, 11].

Mechoulam *et al.* described that CBD, in the presence of boron trifluoride etherate in methylene chloride, rapidly isomerized to (−)-*trans*-Δ^9-THC (60% yield) and Δ^8-iso-THC (13%) [12].

Alternatively cannabidiol can be converted quantitatively into delta-8-tetrahydrocannabinol by strong acid and then into (−)-*trans*-Δ^9-THC by hydrochlorination and dehydrochlorination [12-17].

Cannabidiol

Strong acid
heat

(-)-*trans*-delta-8-tetrahydrocannabinol

BF$_3$Et$_2$O

HCl
ZnCl$_2$

(-)-*trans*-delta-9-tetrahydrocannabinol

+

(-)-delta-8-iso-tetrahydrocannabinol

potassium-*tert*-amylate

(-)-*trans*-delta-9-tetrahydrocannabinol
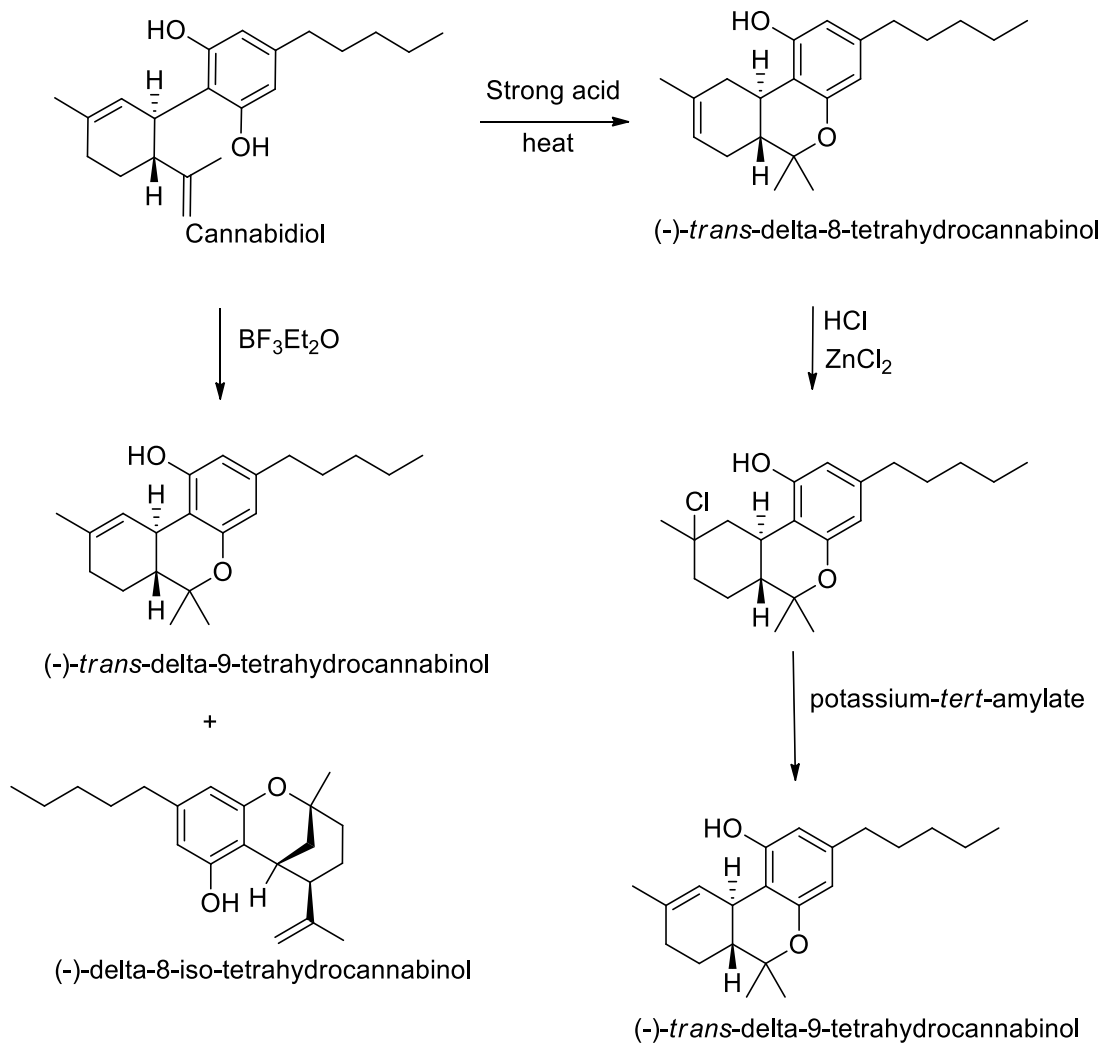
2.4.4   Total synthesis of (–)-trans-Δ^9-THC

After the first synthesis of (±)-*trans*-Δ^9-THC, published by Mechoulam and co-workers [18], a number of stereospecific syntheses were published, such as those by Petrzilka *et al.* [19, 20], by Razdan and Handrick [21], and Gaoni and Mechoulam [6, 11] that are based on the same principle, the condensation of olivetol with an optically pure monoterpene [22-25].

The synthesis of Petrzilka *et al.* demonstrated a facile entry into cannabinoids utilizing (+)-*cis*- or *trans*-*p*-mentha-2,8-dien-l-ol. By condensing with olivetol in the presence of weak and strong acids they obtained (–)-CBD and (–)-Δ^8-THC, respectively. The yield of cannabidiol was 25%, but with a strong

acid, no cannabidiol was isolated and delta-8-tetrahydrocannabinol was obtained in 53% yield. The conversion to (–)-*trans*-Δ^9-THC was carried out by addition of hydrochloric acid (HCl) and dehydrochlorination using potassium *tert*-amylate in benzene obtaining a 100% yield.

(+)-*cis*-*p*-mentha-2,8-dien-1-ol
or
(+)-*trans*-*p*-mentha-2,8-dien-1-ol

olivetol

(-)-*trans*-delta-8-tetrahydrocannabinol

(-)-*trans*-delta-9-tetrahydrocannabinol
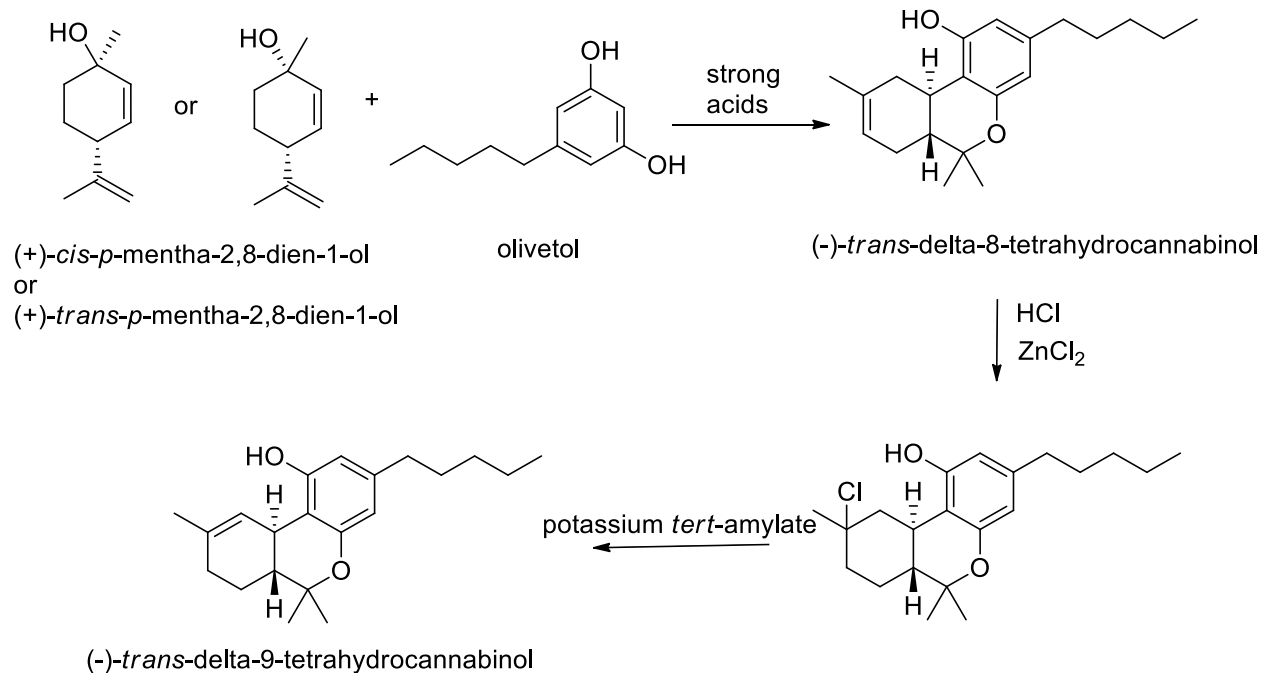
Because of the commercial availability of the starting terpene *cis*/*trans*-*p*-mentha-2,8-dien-l-ol, this route was further developed by Razdan and co-workers for the preparation of (-)-*trans*-Δ^9-THC employing boron trifluoride diethyl etherate (BF$_3$Et$_2$O) in the presence of magnesium sulfate (MgSO$_4$) as the dehydrating agent [26]. By this process (–)-*trans*-Δ^9-THC of very high optical purity was formed in a simple one-step synthesis in 50% yield.

(+)-*cis*-*p*-mentha-2,8-dien-1-ol
or
(+)-*trans*-*p*-mentha-2,8-dien-1-ol

olivetol

(–)-*trans*-delta-9-tetrahydrocannabinol
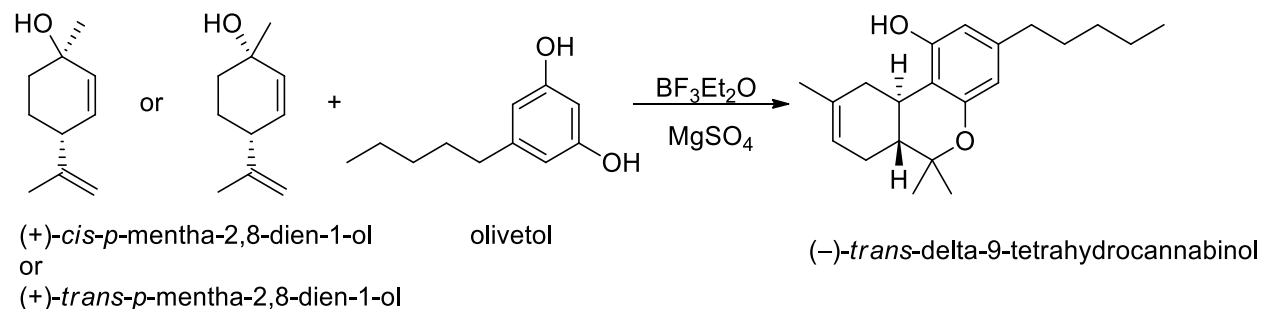
Section 1: Chemistry

Recently, a stereoselective total synthesis of all isomeric forms of Δ^9-THC has been developed by Schafroth *et al.* [5].

2.5   Chemical Properties

i.   (−)-*trans*-Δ^9-THC:

2.5.1   *Melting point*

<25 °C [27]

2.5.2   *Boiling point*

200 °C at 0.02 Torr[1]

2.5.3   *Solubility*

Yalkowsky *et al.* measured a pKa of 10.6 and a solubility in water of 2.8 mg/L at 23 °C [28]. (-)-*trans*-Δ^9-THC is also soluble in alcohol (1 part in 1 part of alcohol); 1 part in 1 part of acetone; 1 part in 3 parts of glycerol. It is also soluble in 0.15 M sodium chloride (0.77 mg/L at 23 °C) and in fixed oils [29].

(-)-*trans*-Δ^9-THC binds to glass (20% at 0.1 µg/mL). Polycarbonate, polypropylene, Teflon and stainless steel containers showed more extensive binding than glass. Degraded rapidly in acidic solution ($t_{1/2}$=1 h at pH 1 and at 55 °C) [30].

Rosenkrantz *et al.* conducted studies of solubility of (−)-*trans*-Δ^9-THC, (−)-*trans*-Δ^8-THC and pure cannabis extract in several solvents like ethanol, acetone, dimethyl sulfoxide (DMSO), chloroform, benzyl alcohol and sesame oil in order to obtain suitable oral and parenteral formulations of cannabinoids. Similar solubility values were obtained for (−)-*trans*-Δ^9-THC, (−)-*trans*-Δ^8-THC and crude cannabis extract in polar solvents. The solubility of (−)-*trans*-Δ^9-THC was in ethanol and acetone greater than 1 g/mL, 0.90 g/mL in benzyl alcohol, 0.30 g/mL in sesame oil, 0.54 g/mL in DMSO, 0.58 g/mL in propylene glycol, 0.39 g/mL in glycerol and 0.28 g/mL in polyoxyethylene monooleate (Tween 80) [31].

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[1] Reported by Chemical Abstract Service (CAS).

2.5.3.1   n-Octanol/water partition coefficients (Po/w)

n-Octanol/water partition coefficients (Po/w) of (−)-*trans*-Δ^9-THC, as measured by shake-flask methods, span from 6,000 [32] to 60,000, as estimated by Roth and Williams [30].

Brian *et al.* calculated the Po/w of (−)-*trans*-Δ^9-THC and (−)-*trans*-Δ^8-THC by two procedures: reverse-phase high-pressure liquid chromatographic (HPLC) and computer calculation.   As expected, the position of the double bond in either position 8 or 9 had only a poor effect on the Po/w. Based on the molecular structure, the log Po/w obtained for (−)-*trans*-Δ^9-THC by computer calculation was 7.18, which is in close agreement with the log Po/w of 6.93 as determined by HPLC. This very high value of log Po/w indicated an extreme lipophilicity [33].

2.5.3.2   Optical Rotatory Power

Reports vary from −148 to −161.8:

- −148: (*c.* 0.35,CHCl$_3$, wavelength: 589.3 nm) [34]
- −150.5: (CHCl$_3$, Temp: 20 °C)[10]
- −161.8: (*c.* 1.0, CHCl$_3$) [5]

2.5.3.3   Stability

When stored, (−)-*trans*-Δ^9-THC decomposes and becomes reddish [4]. It is unstable in air, light, and acidic media and at high temperatures. (−)-*trans*-Δ^9-THC is more stable in ethanol than in carbon tetrachloride or hexane. Thin films of (−)-*trans*-Δ^9-THC are less stable than (−)-*trans*-Δ^9-THC in solutions. Stability is not improved by adding antioxidants. The major product of (−)-*trans*-Δ^9-THC decomposition is cannabinol (CBN) and the minor product is (−)-*trans*-Δ^8-THC. Due to its high lipid/aqueous partition coefficient, (−)-*trans*-Δ^9-THC has a higher affinity for biomembranes than for aqueous media [3, 6, 35].

2.5.3.4   Chemical characterization

^{1}H NMR (400 MHz, CDCl$_3$)

δ = 6.32 – 6.28 (m, 1H), 6.27 (d, J = 1.6 Hz, 1H), 6.14 (d, J =1.6 Hz, 1H), 4.71 (s, 1H), 3.25 – 3.15 (m, 1H), 2.48 – 2.38 (m, 2H), 2.21 – 2.11 (m, 2H), 1.95– 1.85 (m, 1H), 1.71 – 1.67 (m, 4H), 1.60 – 1.51 (m, 2H), 1.41 (m, 4H), 1.33 – 1.24 (m, 4H), 1.09 (s, 3H), 0.91 – 0.84 (m, 3H)

^{13}C NMR (101 MHz, CDCl$_3$)

δ = 154.9, 154.3, 143.0, 134.6, 123.8, 110.3, 109.2, 107.7, 77.4, 46.0, 35.6, 33.7, 31.7, 31.3, 30.8, 27.7, 25.2, 23.5, 22.7, 19.4, 14.2

IR (neat, v_{max}/cm^{-1})

3392, 2927, 2858, 1624, 1578, 1425, 1365, 1331, 1268, 1234, 1183, 1129, 1113, 1038, 878

$[α]^{25}_D$ = −161.8 (*c.* 1.0, CHCl$_3$) [5]

  ii. (+)-*trans*-Δ^9-THC:

Melting point: N/A

Boiling point: N/A

Solubility: N/A

Stability: N/A

2.5.3.5 Chemical characterization

^{1}H NMR (400 MHz, CDCl$_3$)

δ = 6.32 – 6.28 (m, 1H), 6.27 (d, J = 1.6 Hz, 1H), 6.14 (d, J =1.6 Hz, 1H), 4.71 (s, 1H), 3.25 – 3.15 (m, 1H), 2.48 – 2.38 (m, 2H), 2.21 – 2.11 (m, 2H), 1.95– 1.85 (m, 1H), 1.71 – 1.67 (m, 4H), 1.60 – 1.51 (m, 2H), 1.41 (m, 4H), 1.33 – 1.24 (m, 4H), 1.09 (s, 3H), 0.91 – 0.84 (m, 3H)

^{13}C NMR (101 MHz, CDCl$_3$)

δ = 154.9, 154.3, 143.0, 134.6, 123.8, 110.3, 109.2, 107.7, 77.4, 46.0, 35.6, 33.7, 31.7, 31.3, 30.8, 27.7, 25.2, 23.5, 22.7, 19.4, 14.2

IR (neat, v_{max}/cm^{-1})

3392, 2927, 2858, 1624, 1578, 1425, 1365, 1331, 1268, 1234, 1183, 1129, 1113, 1038, 878

$[\alpha]^{25}_D$ = +159.1 (*c*. 1, CHCl$_3$) [5]

    iii.   (−)-*cis*-Δ^9-THC:

Melting point: N/A

Boiling point: N/A

Solubility: N/A

Stability: N/A

Chemical characterization

^{1}H NMR, ^{13}C NMR and IR data were identical with that of the (+)-*trans*-Δ^9-THC.

$[\alpha]^{25}_D$ = −95.0 (*c*. 1.0, CHCl$_3$) [5]

    iv.   (+)-*cis*-Δ^9-THC:

Melting point: N/A

Boiling point: N/A

Solubility: N/A

Stability: N/A

2.5.3.6   Chemical characterization

^{1}H NMR (400 MHz, CDCl$_3$)

δ = 6.25 (d, J = 1.6 Hz, 1H), 6.23 − 6.19 (m, 1H), 6.13 (d, J = 1.6 Hz, 1H), 4.75 (s, 1H), 3.56 (t, J = 5.6 Hz, 1H), 2.47 − 2.39 (m, 2H), 2.06 − 1.88 (m, 3H), 1.75 − 1.70 (m, 1H), 1.70 − 1.67 (bs, 3H), 1.59 − 1.52 (m, 2H), 1.5 - 1.42 (m, 1H), 1.39 (s, 3H), 1.34 − 1.28 (m, 4H), 1.27 (s, 3H), 0.90 − 0.86 (m, 3H)

^{13}C NMR (101 MHz, CDCl$_3$)

δ = 154.9, 154.0, 142.6, 135.2, 122.1, 110.2, 109.6, 108.1, 76.3, 40.2, 35.6, 31.7, 31.7, 30.7, 29.9, 26.1, 25.5, 23.8, 22.7, 20.8, 14.2

IR (neat, vmax /cm-1) 3395, 2927, 2856, 1622, 1577, 1425, 1379, 1366, 1263, 1236, 1157, 1136, 1112, 1035, 889

$[\alpha]^{25}_D$ = +91.7 (*c.* 1.0, CHCl$_3$) [5]

2.6   Identification and Analysis

Synthetic (−)-*trans*-Δ^9-THC was characterized and ^{1}H NMR properties [36, 37], ^{13}C NMR properties [36-39], mass properties [36, 40-57] and ultraviolet (UV) and visible properties [56, 58] are reported.

Recently, Schafroth *et al.* synthesized all stereoisomeric forms of Δ^9-THC and optical rotatory power, ^{1}H NMR, ^{13}C NMR, IR and chromatographic enantioseparation of each stereoisomer was reported [5].

Color tests are described in "Recommended methods for the identification and analysis of cannabis and cannabis products" edited by United Nations office on drug and crime [59]. They are the Fast Corinth V salt test, Fast Blue B salt test and Rapid Duquenois test (Duquenois-Levine test) [59]. The positive results to color tests are only presumptive test and it is therefore mandatory for the analyst to confirm such results using additional analysis like chromatographic analysis.

Several analytical methods are reported regarding (−)-*trans*-Δ^9-THC qualitative and quantitative determination in different matrices such as cannabis inflorescence, cannabis extracts and biological fluids. Chromatographic methods are the most employed coupled to several detection techniques such as UV

and mass spectrometry (MS) [60]. Based on the specific matrix available, specific sample pre-treatment and chromatographic method should be followed. In general, the chromatographic techniques can be divided into:

2.6.1 Thin-layer chromatography (TLC)

It is quite difficult to separate (−)-*trans*-Δ^8-THC from (−)-*trans*-Δ^9-THC employing a normal and polar stationary phases [56]. A two dimensional TLC method has been developed with the advantage to obtain a better resolution between the two isomers [61].

2.6.2 Gas chromatographic method with mass spectrometry (GC-MS) or flame ionization detection (GC-FID)

These methods are widely employed in several laboratories and permit to analyse (−)-*trans*-Δ^9-THC with or without preliminary derivatization [56, 62]. Hazekamp *et al.* also developed a GC-MS method that easily distinguished (−)-*trans*-Δ^9-THC from its isomer (−)-*trans*-Δ^8-THC [56]. GC methods are generally employed for both plant material and biological matrices with an appropriate sample pre-treatment [60].

2.6.3 Liquid chromatography (LC)

LC methods are generally coupled to ultraviolet (LC-UV) and/or mass spectrometry (LC-MS) detection. They offer the advantage of a very high sensitivity without a derivatization step [63-67]. LC methods are widely employed for both plant material and biological matrices with an appropriate sample pre-treatment [60]. As for GC-MS, (−)-*trans*-Δ^9-THC from its isomer (−)-*trans*-Δ^8-THC can be easily separated by LC-UV [56].

3.   Ease of Convertibility Into Controlled Substances

The only controlled substance that $(-)$-*trans*-Δ^9-THC can be converted into is its isomer $(-)$-*trans*-Δ^8-THC, which is in Schedule I of the 1971 Convention. The conversion reaction is reported in the literature and involves the treatment of $(-)$-*trans*-Δ^9-THC with an acid resulting in an equilibrium mixture containing approximately 3% of the $(-)$-*trans*-Δ^9- and 97% of the more thermodynamically stable $(-)$-*trans*-Δ^8-THC isomer [68, 69].

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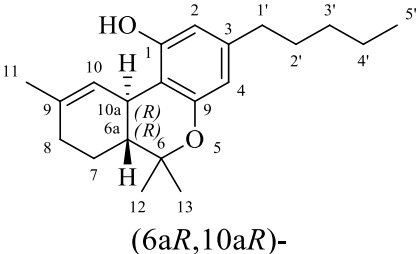
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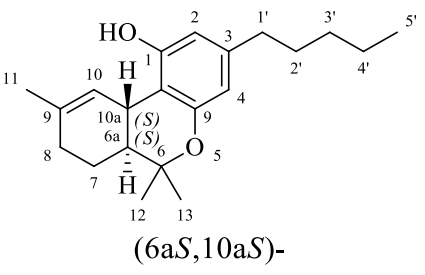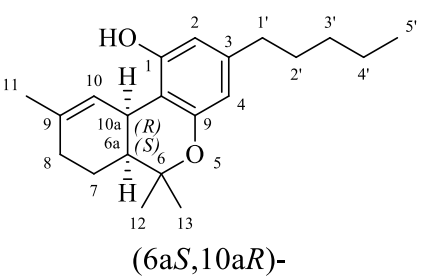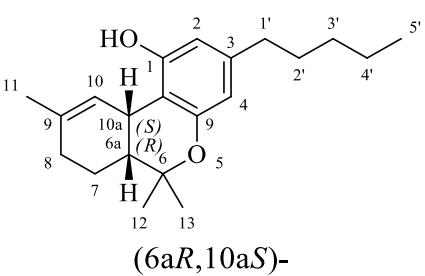
Table 1: Stereoisomers of delta-9-THC

Short name	Full name (*have IUPAC name and add the CA index names*	Alternative names (*add footnotes from man text)which are normally lettered in table but as a largely a text table numbers perhaps better*	Natural occurrence	CAS Registry Number	Structure

| (−)-trans-Δ⁹-THC | **IUPAC name**: (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA index name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aR)- | 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)-

Cannabinol, tetrahydro-(6CI)

(6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

(−)-trans-Δ⁹-THC

(−)-trans-Δ⁹-Tetrahydrocannabino

(−)-Δ⁹-Tetrahydrocannabinol

(−)-Δ⁹-trans-Tetrahydrocannabinol

(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol

Abbott 40566

Cannabinoids, THC

Dronabinol

Marinol

NSC 134454

Namisol

QCD 84924

SP 104

THC

Tetrahydrocannabinol

trans-(−)-Δ⁹-Tetrahydrocannabinol trans-

Δ⁹-Tetrahydrocannabinol

Δ⁹-THC [4]

Δ⁹-Tetrahydrocannabinol [4]

Δ⁹-trans-Tetrahydrocannabinol [4]

Cannabinol, Δ¹-tetrahydro-(7CI) [4]

(−)-3,4-trans-Δ¹-Tetrahydrocannabinol [4]

(−)-trans-Δ¹-Tetrahydrocannabinol [4]

(−)-Δ¹-Tetrahydrocannabinol [4]

(1)-Δ¹-Tetrahydrocannabinol

l-trans-Δ⁹-Tetrahydrocannabinol

l-Δ¹-trans-Tetrahydrocannabinol

Δ¹-THC

Δ¹-Tetrahydrocannabinol | Yes | 1972-08-3 |

(6aR,10aR)- |

30

(+)-*trans*-Δ⁹-THC	***IUPAC name***: (6aS,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name:*** 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6a,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*,10a*S*)-	6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (+)- (8CI)[4] 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-*trans*)-[4] (6*aS*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4] (+)-*trans*-Δ⁹-Tetrahydrocannabinol[4] (+)-Δ¹-Tetrahydrocannabinol[4] (+)-Δ⁹-THC[4] (+)-Δ⁹-Tetrahydrocannabinol[4] *d*-Δ⁹-Tetrahydrocannabinol[4] *trans*-(+)-Δ⁹-Tetrahydrocannabinol [4]	No	17766-02-8	 (6a*S*,10a*S*)-
(−)-*cis*-Δ⁹-THC	***IUPAC name***: (6aS,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name:*** 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS,10aR)-	6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-*cis*)-[4] (6*aS*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4] *cis*-Δ⁹-Tetrahydrocannabinol [4]	No	43009-38-7	 (6a*S*,10a*R*)-
(+)-*cis*-Δ⁹-THC	***IUPAC name***: (6aR,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name:*** 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,	6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-*cis*)-[4] (6*aR*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4]	No	69855-10-3	 (6a*R*,10a*S*)-

	9-trimethyl-3-pentyl-, (6*aR*, 10*aS*)-				

Delta-9-tetrahydrocannabinol

Section 2: Pharmacology

Contents

1. General Pharmacology

The primary psychoactive constituent occurring naturally in the *Cannabis sativa* plant is Δ^9-tetrahydrocannabinol (Δ^9-THC), which may also be synthesized for medical (e.g., dronabinol) or research use. Stereochemical variants of Δ^9-THC include the following:

- (-)-trans-Δ^9-THC (also known as dronabinol)

- (+)-trans-Δ^9-THC

- (-)-cis-Δ^9-THC

- (+)-cis-Δ^9-THC

With exception of research designed to examine the effects of stereoisomers specifically, many articles did not specify the form of Δ^9-THC that was used in the study. In the pharmacology pre-review sections, the stereoisomer name is provided when it was mentioned. When the article refers to use of "Δ^9-THC" and does not specify a stereoisomer, Δ^9-THC is used in the text. However, (-)-trans-Δ^9-THC is the most likely referent in these papers for several reasons: (1) it is the naturally occurring optical isomer present in the plant; (2) this stereoisomer is provided by the United States National Institute on Drug Abuse (NIDA) Drug Supply Program to researchers in the U.S. who request "Δ^9-THC" for their preclinical research; and (3) cannabimimetic psychoactivity is selective for this (-)-isomer as compared to the (+)-isomers. Studies that examined the effects of specific stereochemical variants are mentioned at the end of each pharmacology section.

1.1 Routes of administration and dosage

Δ^9-THC is highly lipophilic and is readily absorbed and distributed to the brain and other organs following many routes of administration in animals, including intraperitoneal (i.p.), oral (p.o.), intramuscular (i.m.), intravenous (i.v.), and inhalation. In humans, the predominant route of administration of Δ^9-THC that is not contained in or extracted from the cannabis plant (covered in separate pre-reviews) is oral (i.e., dronabinol). Therapeutic indications for dronabinol (Marinol®) include treatment of anorexia caused by Acquired Immune Deficiency Syndrome (AIDS) and treatment of chemotherapy-induced nausea and vomiting that is not remedied by standard antiemetics. Dronabinol capsules are available in concentrations of 2.5, 5 and 10 mg. Based upon full prescribing information for patients in the United States (U.S.) that was approved by the U.S. Food and Drug Administration (FDA) [available on the manufacturer's website (http://www.rxabbvie.com/)], the starting dosage for AIDS wasting is 2.5 mg twice daily one hour

before lunch and dinner whereas the starting dosage for chemotherapy-induced nausea is 5 mg/m^2 in intervals before and after chemotherapy for a total of 4 to 6 daily doses. Abuse- or dependence-related research use of dronabinol in humans generally employs bolus oral doses that are substantially higher, as described in sections 7B and 8B of this pre-review.

1.1.1 Stereochemical Variants

With exception of dronabinol (as described above), the stereochemical variants of Δ^9-THC are not routinely administered.

1.2 Pharmacokinetics

In humans, the predominant route of administration of Δ^9-THC that is not contained in or extracted from the cannabis plant is oral (i.e., dronabinol). For this reason, discussion of its pharmacokinetics will concentrate on the oral route of administration. Two excellent comprehensive reviews served as the basis for much of this section.[1, 2]

Compared to absorption of Δ^9-THC in smoked cannabis, absorption of Δ^9-THC following oral ingestion is slow and maximal plasma levels are lower, typically resulting in flatter concentration-time curves.[2] Peak plasma levels typically occur in 60-120 minutes after ingestion; however, delays of up to 4-6 hours have also been reported.[1] Rate of absorption may be affected by dose, vehicle, degradation of the drug in the gut, individual differences in physiology, and the presence/absence of food.[2, 3] Estimated bioavailability averages 6%, with considerable variability among individuals.[4] Ingestion is accompanied by significant first-pass metabolism in the liver, further decreasing the amount of Δ^9-THC that reaches sites of action.

Due to its high lipophilicity, Δ^9-THC is highly bound to plasma proteins and is readily distributed to highly vascularized tissues (e.g., liver, heart, lung) after absorption.[1] Consequent to significant first-pass metabolism, plasma-protein binding, and rapid distribution to tissues, plasma levels of Δ^9-THC following oral administration fall rapidly, even as pharmacological effects (including centrally mediated subjective effects) continue.[1, 2, 5] The prolonged cannabinoid behavioral effects, which occur despite reduced Δ^9-THC plasma levels, may result from slow elimination of Δ^9-THC from the brain, coupled with the cannabimimetic effects of its highly penetrant and equipotent active metabolite, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC).[1, 5] Body fat also serves as a storage reservoir for Δ^9-THC and its metabolites, as Δ^9-THC is eliminated from fat tissues even more slowly than from brain.[1]

Metabolism of orally administered Δ^9-THC occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified.[1] Hydroxylation of the C-11 site to form 11-OH-Δ^9-THC is the initial step of the biotransformation in most species, including humans.[6, 7] This major metabolite is psychoactive, as indicated by its cannabimimetic effects in mice,[8] its substitution for Δ^9-THC in rat drug discrimination,[9] and its similar psychological effects in men.[5, 10] Data from early studies suggested that 11-OH-Δ^9-THC may have greater brain penetrance than Δ^9-THC.[1] Further, whereas cannabis smoking results in low brain levels of 11-OH-Δ^9-THC (vs Δ^9-THC), approximately equal concentrations of the parent compound and its psychoactive metabolite have been observed following oral administration.[2] Although hydroxylation of Δ^9-THC at C-11 to form 11-OH-Δ^9-THC is most common, hydroxylation may also occur at C-8, resulting in formation of 8α-OH-THC and 8β-OH-THC in rodents[6] and 8α-OH-THC in human hepatic microsomes.[11] I.v. administration of the epimers to a small sample of men revealed that both epimers were active, but potency of the 8α-epimer exceeded that of the 8β-epimer.[12] The primary CYP isoenzymes that catalyze the hydroxylation reactions are CYP2C9 and CYP3A4.[11, 13] A secondary metabolite, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (11-COOH-Δ^9-THC or THC-COOH), is formed through oxidation of 11-OH-Δ^9-THC.[14] THC-COOH lacks cannabimimetic effects and is further metabolized to its glucuronide conjugate, which is water soluble and excreted in urine.[2, 13] Due to its extensive metabolism, relatively little Δ^9-THC is eliminated from the body unchanged. Δ^9-THC is excreted primarily in the feces (65-80%) and in the urine (20-35%).[1]

1.2.1 Stereochemical Variants

In most of the studies described in this section, the material evaluated was referred to as "Δ^9-THC," without reference to stereochemical variants. However, (-)-trans-Δ^9-THC (dronabinol) is the naturally occurring isomer and, likely was the tested substance. The metabolism of (+)-trans-Δ^9-THC was reported in a single study.[15] Similar to the (-)-trans-isomer, hydroxylation was a primary mechanism in the biotransformation of (+)-trans-Δ^9-THC. In this initial step, (+)-trans-Δ^9-THC was converted to 11-OH-(+)-trans-Δ^9-THC. Hydroxylation at C-8 was less prominent for (+)-trans-Δ^9-THC. Further, unlike with 11-OH-(-)-trans-Δ^9-THC, oxidation of 11-OH-(+)-trans-Δ^9-THC to its carboxylic acid (i.e., THC-COOH) was minimal. Research on the pharmacokinetics of (-)- and (+)-cis-Δ^9-THC was not found.

Section 2: Pharmacology

1.3 Pharmacodynamics

When administered to animals, Δ^9-THC produces characteristic profile of pharmacological effects which includes a tetrad of effects in mice and rats (locomotor suppression, antinociception, hypothermia and ring/bar immobility), discriminative stimulus effects (rats, mice, pigeons, rhesus monkeys), reinforcing effects (squirrel monkeys), and static ataxia (dogs).[16-18] These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.[19] Within this endocannabinoid system, two cannabinoid receptors, CB_1 and CB_2, have been identified.[20, 21] While CB_1 receptors are widespread and abundant in the brain and periphery, CB_2 receptors are confined primarily to the periphery,[22] although recent evidence suggests that CB_2 receptors may be present in the brain under certain conditions.[23] Δ^9-THC is a partial agonist at both types of cannabinoid receptors, at approximately equal affinities (K_i = 41 and 36 nM for CB_1 and CB_2 receptors, respectively).[24] Its psychoactivity is mediated via activation of CB_1 receptors in the brain in a manner resembling activation by their endogenous ligands (e.g., anandamide and 2-arachidonoylglycerol). For example, research has shown that the discriminative stimulus effects of Δ^9-THC in animals were reversed by pre-injection with rimonabant, a selective CB_1 receptor antagonist, but not by injection with SR144528, selective CB_2 receptor antagonist.[25] Similarly, the reinforcing effects of THC in squirrel monkeys were reversed by rimonabant,[26] as were its antinociceptive, hypothermic and cataleptic effects in rodents[27] and its induction of static ataxia in dogs.[18] Antagonists of other major neurotransmitter systems (e.g., dopamine, acetylcholine, norepinephrine, mu opioid) did not alter the discriminative stimulus effects of Δ^9-THC in rats.[9] Consistent with these in vivo results, Δ^9-THC does not have significant affinity for non-cannabinoid receptors of these major systems.[28] In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64% Δ^9-THC,[29] suggesting that the antagonism results from preclinical Δ^9-THC antagonism experiments are translational.

While Δ^9-THC produces its characteristic pharmacological effects via activation of CB_1 and CB_2 receptors, the brain's endocannabinoid system has extensive interconnections with a variety of other neurotransmitter systems, including dopamine, GABA, glutamate, opioid, and norepinephrine.[30-33] Hence, activation of this system through exogenous administration of Δ^9-THC may have widespread indirect effects on modulatory endocannabinoid-induced regulation of these other neurotransmitters.[34] Of note, similar to the action of many other drugs of abuse, acute administration of Δ^9-THC induces dopamine efflux in reward-related brain areas.[31] In contrast,

withdrawal from Δ^9-THC after chronic administration is associated with decreased activation of dopamine neurons.[35, 36]

1.3.1 Stereochemical Variants

Research on the pharmacodynamics of the stereochemical variants of Δ^9-THC has not been reported (with exception of dronabinol, as described above).

2. Dependence Potential

2.1 Animal Studies

Maldonado[37] has provided an excellent summary of research on the dependence potential of Δ^9-THC in animals. As noted in his review, rapid and profound tolerance develops to numerous acute preclinical effects of Δ^9-THC following chronic administration. Pharmacokinetics plays only a minor role in the development of cannabinoid tolerance. Rather, tolerance to Δ^9-THC's centrally mediated effects appears to be primarily pharmacodynamic in nature and is accompanied by substantial downregulation and desensitization of brain CB_1 receptors.

In contrast, Δ^9-THC-induced physical dependence is less robust. Several studies noted the lack of somatic signs of withdrawal following abrupt termination of chronic dosing with Δ^9-THC in male rodents, as reviewed in [37, 38]. Similarly, female rodents also exhibit few somatic signs of withdrawal after termination of chronic Δ^9-THC treatment.[39] In rhesus monkeys, however, cessation of Δ^9-THC treatment resulted in decreases in responding for food reinforcement.[40] These results suggest that spontaneous withdrawal from Δ^9-THC produces more subtle changes in behavior that contrast with the prominent physical signs observed with some other abused substances (e.g., opioids, alcohol).

Whereas only weak physical signs of withdrawal are observed with spontaneous termination of repeated Δ^9-THC administration, antagonist-precipitated withdrawal is associated with more pronounced signs. In rodents, rimonabant administration induces somatic signs such as wet dog shakes, paw tremors, facial rubbing and ataxia as well as behavioral signs such as suppression of operant responding for food.[39, 41-46] Rimonabant-precipitated withdrawal has also been reported in rhesus monkeys and in dogs.[18, 47]

2.1.1 Stereochemical Variants

Research on the dependence potential of the stereochemical variants of Δ^9-THC in animals has not been reported.

2.2 Human Studies

Limited research has examined the dependence potential of Δ^9-THC specifically (versus cannabis). Early work found that oral administration of Δ^9-THC (10-30 mg) every four hours up to a total daily dose of 210 mg produced reliable acute ratings of "high" and increases in heart rate that dissipated as time elapsed and with repeated administration, suggesting the development of rapid

tolerance.[48] A probe test with a marijuana cigarette during the repeated dosing regimen indicated cross-tolerance also occurred in the participants. During placebo substitution intervals, symptoms of withdrawal were observed, including hyperactivity, increased salivation, irritability, and marked changes in sleep architecture. With exception of sleep disruption (which lasted for up to seven nights), most withdrawal symptoms were alleviated within 96 hours or immediately if participants re-administered Δ^9-THC.

A later study with lower Δ^9-THC doses (80-120 mg daily, p.o.) demonstrated similar development of tolerance to the subjective effects of Δ^9-THC, but not to its appetite enhancing effects.[49] Abrupt cessation of administration after a 4-day repeated dosing regimen resulted in symptoms of withdrawal, including irritability, restlessness, and sleep disruption. In contrast, when the duration of repeated oral Δ^9-THC administration was shortened to 3 days, development of tolerance and physical dependence no longer occurred.[50] Notably, in all of these laboratory-based studies, oral Δ^9-THC doses greatly exceeded recommended dronabinol dosage for the treatment of AIDS-associated wasting and chemotherapy-induced nausea.

2.2.1 Stereochemical Variants

Research on the dependence potential of the stereochemical variants of Δ^9-THC in humans has not been reported.

3. Abuse Potential

3.1 Animal Studies

In animals, the abuse potential of Δ^9-THC has been evaluated in i.v. self-administration and drug discrimination procedures. Because early attempts to train animals to self-administer Δ^9-THC did not result in reliable i.v. self-administration,[51, 52] reviews written during the 1980s and 1990s commonly noted that cannabinoids were "false negatives" in the self-administration model.[53] Then, in 2000, successful acquisition of Δ^9-THC self-administration was described in squirrel monkeys previously trained to self-administer i.v. cocaine.[54] Investigators from the same lab systematically replicated this finding in drug-naïve squirrel monkeys.[55] These studies showed that Δ^9-THC produced a typical U-shaped dose-effect function over a dose range of 1-8 μg/kg/infusion (i.v.), with peak responding at 4 μg/kg/infusion.[56] In several follow-up studies from this lab, the endocannabinoids, anandamide and 2-arachidonoylglycerol, were shown to be reinforcing in Δ^9-THC-trained monkeys and the reinforcing effects of Δ^9-THC were reversed by rimonabant.[26, 57, 58] In rats, investigators have continued to note difficulties in training a robust i.v. Δ^9-THC self-administration,[59, 60] although self-administration of the synthetic aminoalkylindole cannabinoid, WIN55,212-2, has been reported in at least two labs.[60-62]

In contrast with its variable reinforcing effects in the self-administration model, Δ^9-THC produces robust discriminative stimulus effects in several species, including rats (i.p.),[9] rhesus monkeys (i.m.),[63, 64] mice (i.p.),[65, 66] and pigeons (i.m.).[67] In rodents and/or rhesus monkeys, full substitution for Δ^9-THC has been demonstrated for cannabinoids that have been reported to be "marijuana-like" in humans, including Δ^8-THC (i.p. in rats; i.m. in rhesus monkeys and pigeons), cannabinol (i.p. in rats; i.m. in pigeons), hashish (smoke exposure in rats), CP55,940 (i.m. in rhesus monkeys; i.p. in rats), WIN55,212-2 (i.m. in rhesus monkeys; i.p. in rats), and an array of abused synthetic cannabinoids (e.g., JWH-018, XLR-11, UR-144, AB-CHMINACA; i.p. in rodents; i.m. in rhesus monkeys).[9, 63, 64, 68-73] Conversely, cannabidiol (route), a cannabis plant-derived constituent that does not have psychoactive effects in humans, fails to substitute in pigeons (i.m.) or rats (i.p.) trained to discriminate Δ^9-THC from vehicle.[9, 69, 74] Further, pharmacological specificity is indicated by the lack of generalization from THC observed after administration of drugs from a wide variety of non-cannabinoid classes, including antipsychotics, opioid (mu, delta, and kappa) agonists, tricyclic antidepressants, dissociative anesthetics, barbiturates, stimulants, muscarinic agonists, nicotine, and GABA agonists.[9, 64, 68, 75, 76] Although partial substitution has been reported with

diazepam, this effect is accompanied by significant decreases in overall responding and cross-substitution in rats trained to discriminate diazepam from vehicle does not occur.[77] Δ^9-THC's discriminative stimulus effects are attenuated by prior administration of a selective CB_1 receptor antagonist (e.g., rimonabant),[78] but not by the selective CB_2 receptor antagonist SR144528.[25] These effects are also not reversed by antagonists of other major neurotransmitter systems, including dopamine, acetylcholine, norepinephrine, and mu opioid.[9, 68, 75]

Cross-substitution of Δ^9-THC in animals trained to discriminate other cannabinoids also has been reported. Δ^9-THC generalizes from Δ^8-THC, CP55,940, and JWH-018 in rodents.[79-81] Δ^9-THC has been evaluated in several discrimination procedures in which non-cannabinoid drugs served as the training stimulus. The results of these studies show that it did not substitute for diazepam, midazolam, mephedrone, cocaine, d-amphetamine, or phencyclidine,[77, 82-86] providing additional evidence of the pharmacological selectivity of Δ^9-THC's discriminative stimulus effects.

3.1.1 Stereochemical Variants

The most commonly cited source of Δ^9-THC used in the research described above was the NIDA Drug Supply Program which provides synthetic (-)-trans-Δ^9-THC to researchers. Limited work has examined specific effects of the other three stereochemical variants of Δ^9-THC. Although early studies reported that the (+)-Δ^9-THC stereoisomers were considerably less potent in vivo than the (-)-Δ^9-THC stereoisomers, these studies were not conducted using optically pure enantiomers.[87, 88] However, as improvements in synthetic methods led to enhanced purity, these initial findings have been upheld. For example, Martin et al.[87] reported that (-)-trans-Δ^9-THC was at least ten-fold more potent in the dog static ataxia model than (+)-cis-Δ^9-THC or (+)-trans-Δ^9-THC, neither of which produced the full syndrome at the highest dose that the limited drug quantities allowed. In addition, (-)-trans-Δ^9-THC exhibited 10-fold greater hypothermic effect in mice and was 100-fold more potent at decreasing schedule-controlled responding in rhesus monkeys than (+)-Δ^9-THC.[87] Similarly, greater potencies were noted for (-)-trans-Δ^8-THC and -11-OH-Δ^8-THC-dimethylheptyl than for their (+)-isomers,[87, 89] suggesting that the psychoactivity of the tetrahydrocannabinols is stereoselective and resides in their naturally occurring (-)-stereoisomers.[88]

3.2   Human Studies

With few exceptions, human studies relevant to the abuse potential of pure or synthetic Δ^9-THC (i.e., excluding cannabis and plant-derived extracts) have used dronabinol and an oral route of

administration. In controlled laboratory settings, self-administration of dronabinol has been demonstrated;[90-92] however, results suggest that it is a weak reinforcer at best. First, self-administration was variable, in that subjects chose to take dronabinol only during about 50% of the opportunities it was offered.[90] Second, if given the opportunity to choose a marijuana cigarette instead of oral Δ^9-THC, 80% of the study participants preferred the marijuana cigarette.[92] In addition, dronabinol does not appear to be abused outside of the laboratory. A multi-method review that incorporated findings from the scientific and product safety literature as well as interviews with physicians and perusal of the popular press revealed little evidence that oral dronabinol was used for non-medical purposes.[93] Phenomena such as "doctor-shopping" or "script-chasing" were not common and dose escalation did not typically occur with continued medicinal administration.[93]

Although oral Δ^9-THC is a weak reinforcer, it has robust subjective effects that resemble those of cannabis. Male and female study participants readily distinguish oral Δ^9-THC (7.5 mg) as being "marijuana-like" and as different from alcohol (0.8 g/kg) or d-amphetamine (20 mg).[94] On a Capsules Rating Form that is sensitive to cannabinoid drugs, Δ^9-THC (dronabinol, 10 and 20 mg) was associated with increased ratings of "strong drug effect," with peak effect occurring at 90 minutes post-administration.[95] Further, when oral or smoked Δ^9-THC was compared directly to cannabis administered via the same route of administration, both Δ^9-THC and cannabis (each containing 8.4 or 16.9 mg Δ^9-THC) produced a similar profile of subjective effects on the Addiction Research Center Inventory, including increased feelings of "drug effect," experience of a "drug high," and increased ratings on the Marijuana scale.[96] Oral administration of Δ^9-THC or cannabis produced greater sedation whereas smoking either substance failed to do so.[96] Both substances produced dose-dependent increases in plasma Δ^9-THC levels, beginning immediately after smoking and at approximately 60 minutes after oral administration.[96] Naltrexone (a mu-opioid receptor antagonist) did not reverse these subjective effects of oral dronabinol.[97]

In addition to evaluation of self-reported subjective effects, dronabinol has been examined in a series of studies using a more traditional drug vs. placebo discrimination procedure, in which participants successfully acquired a discrimination based upon a training dose of 25-30 Δ^9-THC.[98-101] Δ^9-THC produced dose-dependent substitution for the training dose in participants of both sexes[98-101] and self-reported subjective effects resembled those noted in previous studies that relied entirely on survey measures. As in the animal studies, Δ^9-THC discrimination was

pharmacologically selective (to the extent tested), with triazolam (a positive modulator of the GABA-A receptor), hydromorphone (a mu-opioid agonist), and methylphenidate (a dopamine reuptake inhibitor) failing to substitute for Δ^9-THC in the discrimination procedure.[100]

3.2.1 Stereochemical Variants

Research on the abuse potential of the stereochemical variants of Δ^9-THC in humans has not been reported.

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Delta-9-tetrahydrocannabinol

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1. Toxicology

The pharmacological activity of Δ^9-THC is stereoselective: the (-)-trans isomer is 6-100 times more potent than the (+)-trans isomer [1]. The (-)-trans isomer (also known as dronabinol) is found naturally in the plant and most scientific and clinical studies have been conducted with the (-)-trans isomer. Synthetic forms of Δ^9-THC have been produced (eg, Marinol) and are available on prescription in several countries as a treatment for chemotherapy-induced nausea and vomiting and HIV-related wasting [2]. Pure Δ^9-THC is not typically used as a recreational substance, rather being present as the main intoxicating component of smoked cannabis, vaporised cannabis and cannabis extracts and concentrates (see Report 1: Cannabis plant and cannabis resin).

1.1 Lethal dose

The toxicity of Δ^9-THC is very low compared to most other recreational and pharmaceutical drugs. Following oral administration, the median lethal dose (LD_{50}) was 800 mg/kg in rats [3], up to 3000 mg/kg in dogs and up to 9000 mg/kg in monkeys [4]. It has been calculated that a lethal dose in a 70 kg human would be approximately 4 g [5] and that such a dose could not be realistically achieved in a human following oral consumption, smoking or vaporising the substance[6]. The absence of mortality with Δ^9-THC may reflect the low density of cannabinoid CB1 receptors in brainstem regions that control vital cardiovascular or respiratory functions.

1.2 Effects on the cardiovascular system

A recent meta-analysis concluded that acute Δ^9-THC exposure in humans produces tachycardia with an average increase in heart rate of 8 beats per minute (bpm) [7]. The effects of Δ^9-THC on cardiovascular function are generally dose-dependent: a dose of 7.5 mg did not affect heart rate or blood pressure, while 12 mg caused tachycardia (mean increase of 4 bpm) without a change in blood pressure [7]. Tolerance may occur to these effects: an early study administered oral Δ^9-THC to 12 healthy male participants with an escalating dosing regimen over 20 days (up to 210 mg Δ^9-THC per day; 7 x 30 mg oral doses). While Δ^9-THC promoted tachycardia early in the treatment period, at later stages it actually *decreased* supine systolic and diastolic blood pressure and decreased heart rate [8]. This highlights that the hemodynamic effects of Δ^9-THC may vary according to exposure over time. Animal studies have limited relevance to understanding human cardiovascular effects since Δ^9-THC generally promotes bradycardia and hypotension in laboratory animal species, effects that are opposite to those observed in humans.

1.3 Effects on the respiratory system

Δ^9-THC is a bronchodilator with possible benefit in treating asthma ([9-11], reviewed in [12]). On the other hand, *in vitro* studies indicate that Δ^9-THC: reduces the viability of human epithelial lung cells; causes oxidative stress; and suppresses apoptosis and mitochondrial function in these cells [13-15]. Δ^9-THC also induced expression of cytochrome P450 1A1 (CYP1A1) *in vitro*, which activates polycyclic aromatic hydrocarbons and has been linked to lung cancer [16-18]. However, the relevance of these changes to human risk is unknown with no increased lung cancer risk detected in epidemiological studies of cannabis users (see critical review of cannabis and cannabis resin). In fact, Δ^9-THC is considered to have potential therapeutic effects in airway disease by reducing inflammation in airways and increasing lung cancer cell lysis mediated by lymphocyte activated killer cells [19, 20].

1.4 Effects on the immune system

In vitro and *in vivo* animal studies demonstrate that Δ^9-THC can modulate immune function, and this may reflect pharmacological agonist effects on CB2 cannabinoid receptors. For example, Δ^9-THC decreases pro-inflammatory Th1 cytokine responses (e.g. decreasing interferon (IFN)-γ and interleukin (IL)-2 production) and increases anti-inflammatory Th2 cytokine responses (e.g. increasing IL-4 and IL-10 production) (reviewed in [21]). However, the Δ^9-THC doses required in these studies are generally large and may not be relevant to typical human doses [22-24].

Studies administering pure Δ^9-THC to patients provide more relevant insights into the immunomodulatory effects of the drug. In a large RCT involving multiple sclerosis patients given oral Δ^9-THC (up to 25 mg/day for 14 weeks) there were no significant effects observed on serum concentrations of IFNγ, IL-10, IL-12 or C-reactive protein [24]. However, this study may have inadequately underpowered to detect such changes. A 3 week RCT involving 22 immunocompromised HIV patients on antiretroviral therapy given Δ^9-THC (2.5 mg per day) found no effects on: the percentage of CD4+ and CD8+ T cells; resting or activated T cells; natural killer cell number; and on immune responses to *Staphylococcal* enterotoxin B, cytomegalovirus (CMV), phytohemagglutinin, tetanus toxin, or alloantigen [22, 23].

1.5 Mutagenicity

According to a comprehensive assessment by the US National Toxicology Program, Δ^9-THC does not have mutagenic or carcinogenic effects [25]. Δ^9-THC induced sister chromatid exchanges and cell cycle delay at

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the highest dose tested in Chinese hamster ovary cells, however it did not induce chromosomal aberrations. Further, Δ^9-THC was not mutagenic in several bacterial Salmonella typhimurium strains (the Ames test). Cultured human lymphocytes treated with Δ^9-THC (up to 100 µg/ml) for 72 hours showed no induction of chromosomal abnormalities [26]. There was no increase in frequency of micronucleated erythrocytes in the blood of mice administered oral Δ^9-THC up to 500 mg/kg for 13 weeks [25]. Oral administration of Δ^9-THC at doses up to 50 mg/kg/day for 2 years revealed no carcinogenic effects in rats. There was more equivocal evidence for increased neoplastic activity in mice treated with 125 mg/kg/day Δ^9-THC for 2 years due to an increased incidence of thyroid gland follicular cell adenomas. However, this was not dose-dependent, with no increased incidence of adenomas in the 250 and 500 mg/kg/day groups. These are extremely high doses: an oral 125 mg/kg Δ^9-THC dose in mice equates to a 625 mg Δ^9-THC dose in a 60 kg human (the maximum recommended daily dose of dronabinol is 144 mg in a 60 kg human) [2].

1.6 Fertility and teratogenesis

Oral administration of Δ^9-THC in rats (5-25 mg/kg/day) for 77 days reduced the size of the seminal vesicles and seminal fluid volume [2]. Δ^9-THC also decreased spermatogenesis and the number of Leydig cells in the testis. However, sperm count, mating success and testosterone levels were not affected. More recently, Δ^9-THC reduced mouse sperm motility, and a 50 mg/kg dose administered to male mice before mating reduced litter sizes by 20% [27].

Pure Δ^9-THC (dronabinol) use is restricted to a small number of therapeutic applications in humans and epidemiological and pharmacovigilance data do not exist with which to assess its teratogenicity in humans. Δ^9-THC readily crosses the placenta into the blood of the foetus and is secreted in maternal milk during lactation [28-30]. *In vitro* Δ^9-THC reduces the cell turnover of human trophoblasts, the major placental cells [31]. Numerous animal teratogenicity studies were conducted in the 1970's which collectively suggest that Δ^9-THC exposure (at doses up to 400 mg/kg) during gestation may promote subtle reductions in foetal weights and litter numbers, but with no gross physical abnormalities observed [32-35]. Exposure of pregnant animals to Δ^9-THC can affect offspring neurobehavioral development with effects reported on altered locomotor activity, cognitive dysfunction, and vulnerability to drugs of abuse [36-38].

1.7 DUID

Oral Δ^9-THC (dronabinol) is reported to cause driving impairment in both driving simulator and on-road [39-41]. At 10 and 20 mg doses, dronabinol increased standard deviation of lateral position (SDLP), indicative of

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loss of road tracking control, and time to speed adaptation, indicative of increased reaction times in response to a followed vehicle [39]. The impairments were dose-dependent and were observed in occasional and heavy users of cannabis, although effects appeared greater in the occasional users. 25% of the heavy users displayed comparable or worse impairments than those observed at a 0.05 % blood alcohol concentration (BAC).

2. Adverse reactions in humans

Δ^9-THC has very similar pharmacological and subjective effects to cannabis in humans. Users may experience euphoria, laughter and increased loquacity. Δ^9-THC increases appetite, promotes dry mouth and occasional dizziness, and enhances visual, olfactory and auditory perceptions. THC exposure may also cause nausea and vomiting in some users [42]. Δ^9-THC's effects are mostly subject to tolerance with repeated exposure.

Δ^9-THC exposure can cause subtle cognitive deficits such as impaired attention and short-term memory impairment [43]. Higher doses of Δ^9-THC are associated with anxiety, panic, confusion, and disorientation in some users. Δ^9-THC exposure can provoke transient psychosis-like psychological phenomena in some healthy participants [44, 45]. For example, Sherif et al. (2016) showed that intravenous Δ^9-THC increased conceptual disorganization, fragmented thinking, suspiciousness, paranoid and grandiose delusions, and perceptual distortions [46]. However, these effects were modest in magnitude and reversible. In one study of 22 participants, any psychosis-related effects completely resolved and did not prompt hospitalisation [44]. Although, one participant was administered a benzodiazepine to manage their psychological distress.

RCTs in which Δ^9-THC has been sometimes given daily to participants for periods of years, generally report low to moderate toxicity and a low incidence of serious adverse events. One of the largest and longest running trials to date assessed the efficacy of daily, oral Δ^9-THC administration (up to 28 mg/day) for 3 years in multiple sclerosis patients. Δ^9-THC was generally well tolerated in the 329 patients receiving the drug [47] with no difference in the median number of adverse events in the placebo group and Δ^9-THC group. Δ^9-THC-treated patients experienced more dizziness and light-headedness (32% THC group versus 7% in the placebo group), and dissociative thinking or perception disorders (30% Δ^9-THC group versus 4% in the placebo group). Δ^9-THC-treated patients experienced less musculoskeletal pain and aches (15% versus 25% in the placebo group). While there was no greater rate of serious adverse events in the Δ^9-THC group relative to placebo, more participants in the Δ^9-THC group discontinued the trial relative to the placebo group (43% in the Δ^9-THC group versus 24% in the placebo group).

Similar results were observed in another shorter duration trial of 14 weeks in multiple sclerosis patients who received daily oral Δ^9-THC doses of up to 25 mg per day (there were 206 people in the Δ^9-THC group)

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[48]. Δ^9-THC-treated patients were more likely to experience dry mouth (26% in the Δ^9-THC group versus 7% in the placebo group). Diarrhoea was more common in the Δ^9-THC group than the placebo group.

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Delta-9-tetrahydrocannabinol

Section 4: Therapeutic use

Contents

1.   Marketing Authorizations (as a Medicinal Product)

Dronabinol (Marinol®) is produced and sold by AbbVie, Inc. in the United States.

2.   Listing on the WHO Model List of Essential Medicines

Not listed.

3.   Therapeutic Applications

3.1   Extent of Therapeutic Use

As Marinol®, dronabinol (that is synthetically produced, has FDA approval in the United States for the treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatment. Dronabinol is either approved or available under 'special access rules' in the United Kingdom, Scandinavian countries, and most Western European countries. For example, it is approved in Austria, Denmark and Ireland for CINV unresponsive to conventional treatment in oncology and palliative care and for cancer pain in Denmark. In Ireland, dronabinol is approved for appetite stimulation in HIV. Dronabinol can be prescribed for any type of chronic pain and for any condition in palliative care in Germany.[1]

3.2   Epidemiology of Medical Use

It is estimated that over 90% of patients exposed to highly emetogenic chemotherapy and between 30 and 90% of patients exposed to moderately emetogenic chemotherapy will experience acute-phase CINV. Several observational studies have shown that later onset CINV may be incompletely controlled even if acute CINV has been managed.[2] In a study of 1413 patients, 72% of patients reporting vomiting at the first treatment also reported subsequent vomiting; 31% of these patients experienced emesis at all remaining treatments.[3]

Neuropathic pain is common with a global prevalence of 7% to 8%. Approximately 20% of people with cancer have cancer-related neuropathic pain, due to either the disease or its treatment.[4] A systematic review of 19 UK studies found that chronic pain affects between one-third and one-half of the UK's population, almost 28 million adults, though not all of these are neuropathic in origin. Two of the studies reviewed found that over 8% of the entire population was suffering from chronic neuropathic pain.[5]

3.3 Effectiveness of Therapeutic Uses

(See Table 4&5)

3.3.1 Pure delta-9-tetrahydrocannabinol (excluding approved formulations such as Marinol)

3.3.1.1 Abdominal Pain

In 65 participants with chronic abdominal pain after surgery or from chronic pancreatitis, treatment with THC tablets did not produce differences in visual analog scales of chronic pain. No differences were observed on secondary outcome measures, although those receiving THC were more likely to experience adverse events than those receiving placebo.[6] Analysis of the 24 participants with pain from chronic pancreatitis also failed to show a difference between treatment with THC and placebo.[7]

3.3.1.2 Dementia

Pure delta-9-tetrahydrocannabinol has been studied in four randomized controlled trials in participants with dementia. An initial safety crossover study in ten participants with dementia found that treatment with THC was safe in this population; THC did not produce more adverse events than placebo.[8] Two studies evaluating the effects of THC treatment on neuropsychiatric symptoms in dementia found no difference between THC and placebo. In the first study by Van den Elsen et al., a crossover design of 22 participants receiving up to 3 mg of THC daily yielded no difference between THC and placebo in Neuropsychiatric Inventory (NPI) scores.[9] A second randomized, double-blind, placebo-controlled trial in 50 participants by the same group showed that 4.5 mg of THC daily also failed to produce a difference from placebo in NPI scores, nor were there differences in secondary outcome measures of agitation, quality of life, or activities of daily living.[10] A third trial by the same group, a randomized, placebo-controlled, crossover study of THC 3 mg daily in 18 participants with dementia showed that THC had no adverse effect upon balance, gait, and adverse events in this population.[11]

3.3.1.3 Multiple Sclerosis

Amerongen et al. assessed the effects of a pure form of THC on spasticity and neuropathic pain in 24 participants with progressive MS and moderate spasticity. Treatment with THC decreased neuropathic pain immediately after administration but not when measured in daily diaries. A similar pattern was observed with subjective muscle spasticity; the THC group was also significantly more likely to experience adverse events than the placebo group.[12]

3.3.1.4   Nausea and Vomiting

In a randomized, double-blind, placebo-controlled trial of intravenous THC for postoperative nausea and vomiting in 40 participants, THC did not significantly lessen nausea and vomiting compared to placebo. Due to significant side effects--primarily sedation and confusion--and uncertain efficacy for postoperative nausea and vomiting, the study was discontinued after 40 participants.[13]

3.3.1.5   Neuropathic Pain

As mentioned above, treatment with a pure form of THC decreased neuropathic pain immediately after administration but not when measured in daily diaries in 24 participants with progressive MS.[12]

3.3.2   (-)-trans-delta-9-tetrahydrocannabinol (dronabinol in approved formulations such as Marinol)

3.3.2.1   Anxiety Disorder

No studies of cannabis or cannabinoids with anxiety measures as primary outcomes have been conducted. Narang et al. found evidence in a secondary outcome measure that dronabinol reduced anxiety compared to placebo in 30 participants with chronic pain.[14]

3.3.2.2   Amyotrophic Lateral Sclerosis

In a randomized, double-blind, placebo-controlled trial of dronabinol for amyotrophic lateral sclerosis, treatment with dronabinol yielded no reduction in cramps compared to placeo.[15]

3.3.2.3   Anorexia Nervosa

Dronabinol pharmacotherapy induced a small but significant weight gain in 25 women with anorexia nervosa in an add-on, prospective, randomized, double-blind, placebo-controlled crossover study. Dronabinol was safe and well-tolerated in this group, with no difference between dronabinol and placebo in adverse events.[16]

3.3.2.4   Appetite Stimulation in HIV Infection/AIDS

Four studies of dronabinol as pharmacotherapy for appetite stimulation in HIV/AIDS infection led to dronabinol earning FDA approval for this indication. In a randomized, double-blind, placebo-controlled trial of 67 participants with HIV infection, both dronabinol and smoked cannabis produced significantly

greater weight gain than placebo. This safety study also showed that both dronabinol and smoked cannabis were safe in this population and they did not adversely affect viral load in comparison to placebo.[17] Similarly, treatment with dronabinol was associated with significant weight gain in randomized, double-blind, placebo-controlled trials in 12 and 139 participants, respectively (participants in the latter study were HIV patients already diagnosed with anorexia).[18,19] In an open-label trial of 52 participants with HIV infection, dronabinol, alone and in combination with megastrol acetate, was shown to produce significant weight gain.[20] A retrospective chart review of 117 patients with HIV/AIDS who received a mean daily dose of 9.6-10.8 mg/day over 12 months showed that the percentage of patients experiencing loss of appetite decreased significantly from 71% at baseline to 26% at 1 month (p<.001), but there was no significant decrease in nausea (21)

3.3.2.5   Cannabis Use Disorder

Dronabinol has been studied as pharmacotherapy for cannabis use disorder in two large clinical trials from the same investigative team. In a randomized, double-blind, placebo-controlled trial of 156 participants with cannabis use disorder, dronabinol at 20 mg twice daily did not differ from placebo in the proportion of participants who achieved 2 weeks of abstinence or in reduction of cannabis use. The dronabinol group was significantly more likely to stay in treatment and to have fewer cannabis withdrawal symptoms.[22] In another randomized, double-blind, placebo-controlled trial building upon promising human laboratory data, the combination of dronabinol 20 mg three times daily and the alpha-2 agonist lofexifdine, did not produce a significant difference in the proportion of participants who achieved three weeks of abstinence during the maintenance phase of the trial compared to placebo.[23]

3.3.2.6   Chronic Pain

Dronabinol has been studied as an add-on pharmacotherapy chronic pain. Narang et al. carried out a two-phase investigation of dronabinol's efficacy in 30 participants with chronic pain who took opioids for pain management.[2]4 In Phase I, a randomized, double-blind, placebo-controlled single dose crossover human laboratory study, dronabinol decreased pain intensity and increased patient satisfaction compared to placebo, although there was no difference between 10 mg or 20 mg doses of dronabinol. Phase II, an extended open-label trial of dronabinol added to stable doses of opioids, showed that titration of dronabinol led to significant pain relief, reduced pain bothersomeness, and increased satisfaction compared to baseline.[14] This group of investigators also showed that dronabinol had similar psychoactive effects to smoked marijuana during this trial.[25]

3.3.2.7 Dementia

There have been no randomized, double-blind, placebo-controlled trials of dronabinol for dementia. In a retrospective systematic chart review of 40 geriatric inpatients, a mean of 16.88 days of 7.03 mg of dronabinol daily resulted in a significant reduction in the total score on the Pittsburgh Agitation Scale (Wilcoxon z = -5.1705, p<0.0001) (26).

3.3.2.8 Depression

There have been no studies of cannabis or cannabinoids with measures of depression as the primary outcome. One study of dronabinol (n= 30) found no difference between dronabinol and placebo in depression outcomes.[14]

3.3.2.9 Multiple Sclerosis

Dronabinol pharmacotherapy for multiple sclerosis has been studied in five randomized, double-blind, placebo-controlled trials. Three of these trials evaluated its effects upon spasticity in these participants, one assessed neuropathic pain, and one looked at its effects upon disease progression; one of the trials evaluated both spasticity and pain. Two of the spasticity trials, which enrolled 630, and 13 participants, respectively, found that treatment with dronabinol significantly reduced spasticity by self-report.[27,28] Killestein et al. found in 16 participants that dronabinol did not separate from placebo in its effects upon spasticity.[29] Dronabinol's effects upon neuropathic pain in MS patients has been mixed, with Svendsen et al. showing an effect in 24 participants while Schimrigk did not in 240 participants.[30,31] The CUPID trial of 493 participants with primary or secondary progressive MS found no evidence that dronabinol has an effect on MS progression.[32]

3.3.2.10 Neuropathic Pain

As mentioned above, dronabinol's effects upon neuropathic pain in MS patients was mixed: Svendsen et al. showed an effect in 24 participants while Schimrigk et al. and did not in 240 participants.[30,31]

3.3.2.11 Noncardiac Chest Pain

In a randomized, double-blind, placebo-controlled trial of thirteen patients with functional chest pain, treatment with dronabinol 10 mg daily increased pain thresholds significantly and reduced chest pain intensity and odynophagia compared to placebo without a difference in adverse events.[33] An initial randomized, double-blind, placebo-controlled investigation by the same group in the same participants

showed that dronabinol does not affect basic metabolic parameters like body mass index, HDL, triglycerides, and insulin after a treatment period of 28 days, clearing the way for additional studies of dronabinol in this population.[34]

3.3.2.12 Obstructive Sleep Apnea

In the only randomized controlled trial of a cannabinoid as pharmacotherapy for obstructive sleep apnea, dronabinol produced lower scores on the apnea-hypopnea index, improved scores of self-report sleepiness, and greater treatment satisfaction than placebo. There was no difference between dronabinol and placebo in objectives measures of sleepiness or incidence of adverse events.[35]

3.3.2.13 Opioid Use Disorder

Treatment with dronabinol 30 mg daily, when added to a buprenorphine detoxification regimen, significantly reduced the severity of opioid withdrawal symptoms compared to placebo in a randomized, double-blind, placebo-controlled trial of 60 participants with opioid use disorder. The dronabinol group, however, was not more likely to be successfully induced on injectable naltrexone nor were they more likely to complete treatment.[36]

3.3.2.14 Opioid Withdrawal

In an inpatient randomized, double-blind, placebo-controlled trial of dronabinol for opioid withdrawal suppression in twelve participants with opioid use disorder, dronabinol doses from 5 mg to 30 mg failed to significantly suppress symptoms of opioid withdrawal. Dronabinol administration was complicated by dose-dependent increases in euphoria, sedation, and tachycardia. The tachycardia was significant enough for the initial planned maximum dose of 40 mg to be reduced to 30 mg. Furthermore, participants did not prefer dronabinol over placebo and they demonstrated some impairment in cognitive performance after dronabinol administration as well.[37,38]

3.3.2.15 Spasticity

In a retrospective study of dronabinol in 16 children with complex neurological conditions with spasticity, 12 patients were judged by clinical assessment to have improvement in spasticity. The median duration of treatment was 181 days and the median dose required to obtain a therapeutic effect was 0.33 mg/kg/d (39).

3.3.2.16   Tourette Syndrome

In two (n = 12 and 24) randomized, double-blind, placebo-controlled trials of dronabinol in participants with Tourette Syndrome, dronabinol produced either significant improvement in tics or a trend toward such improvement, as well as a significant improvement in obsessive-compulsive behavior in one of the studies.[40,41]

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3.4   Table 4: Randomized Controlled Trials of Delta-9-tetrahydrocannabinol

Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
Pure delta-9-tetrahydrocannabinol	Capsules, Tablets	15 mg/day	Placebo	2	Abdominal pain
		3-4.5 mg/day	Placebo	4	Dementia
		4.5-15 mg/day	Placebo	1	Multiple Sclerosis

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		Maximum 15 mg/day	Placebo	1	Nausea and Vomiting
		4.5-15 mg/day	Placebo	2	Neuropathic Pain
(-)-trans-delta-9-tetrahydrocannabinol (dronabinol)	Capsules (Oral)	20 mg/day	Placebo	1	Anxiety Disorder
		10 mg/day	Placebo	1	Amyotrophic Lateral Sclerosis
					Anorexia
		5 mg/day	Placebo	1	Appetite Stimulation in HIV/AIDS Infection
		2.5- 10 mg/day	Placebo or Megestrol Acetate	4	
					Cannabis Use Disorder
		40-60 mg/day *note: the maximum recommended daily dose for adults is 20 mg. Severe psychotic symptoms are rare at these doses and precise incidence is unknown.	Placebo	2	

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Intervention	Administration Method	Dose Evaluated	Comparator	Number of Studies Described in this Report	Indication
(-)-trans-delta-9-tetrahydrocannabinol (dronabinol)	Capsules (Oral)	10-20 mg/day	Placebo	3	Chronic Pain
		10-20 mg/day	Placebo	1	Depression
		7.5-15 mg/day	Placebo	5	Multiple Sclerosis
		7.5-15 mg/day	Placebo	2	Neuropathic Pain
		10 mg/day	Placebo	2	Noncardiac Chest Pain
					Obstructive Sleep Apnea
		10 mg/ day	Placebo	1	
					Opioid Use Disorder

3.5   Table 5: Randomized Controlled Trials of Delta-9-tetrahydrocannabinol cont.

		30 mg/day	Placebo	1	Opioid Withdrawal
		5-30 mg/day	Placebo	2	Tourette Syndrome
		5-10 mg/day	Placebo	2	

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Delta-9-tetrahydrocannabinol

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Contents

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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 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

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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

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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)

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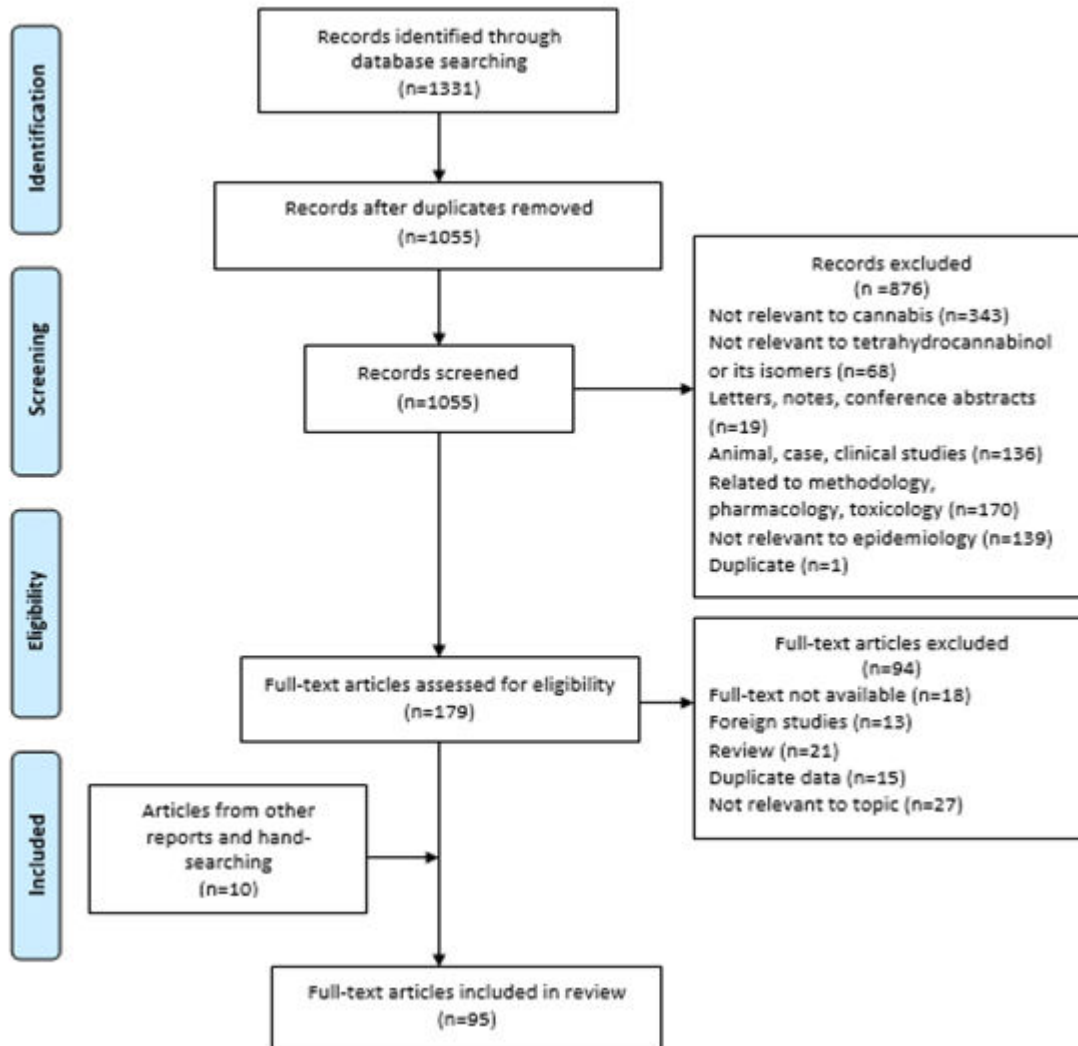
Of 1055 studies retrieved from the search, 179 were included after screening of title and abstract (see Appendix 1 for Reports 3 for details). After full-text screening, 95 studies were included in report 1. Review articles were excluded from analysis but were kept for the background of the report and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

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

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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).

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Figure A2: Revised PRISMA Diagram for Report 3
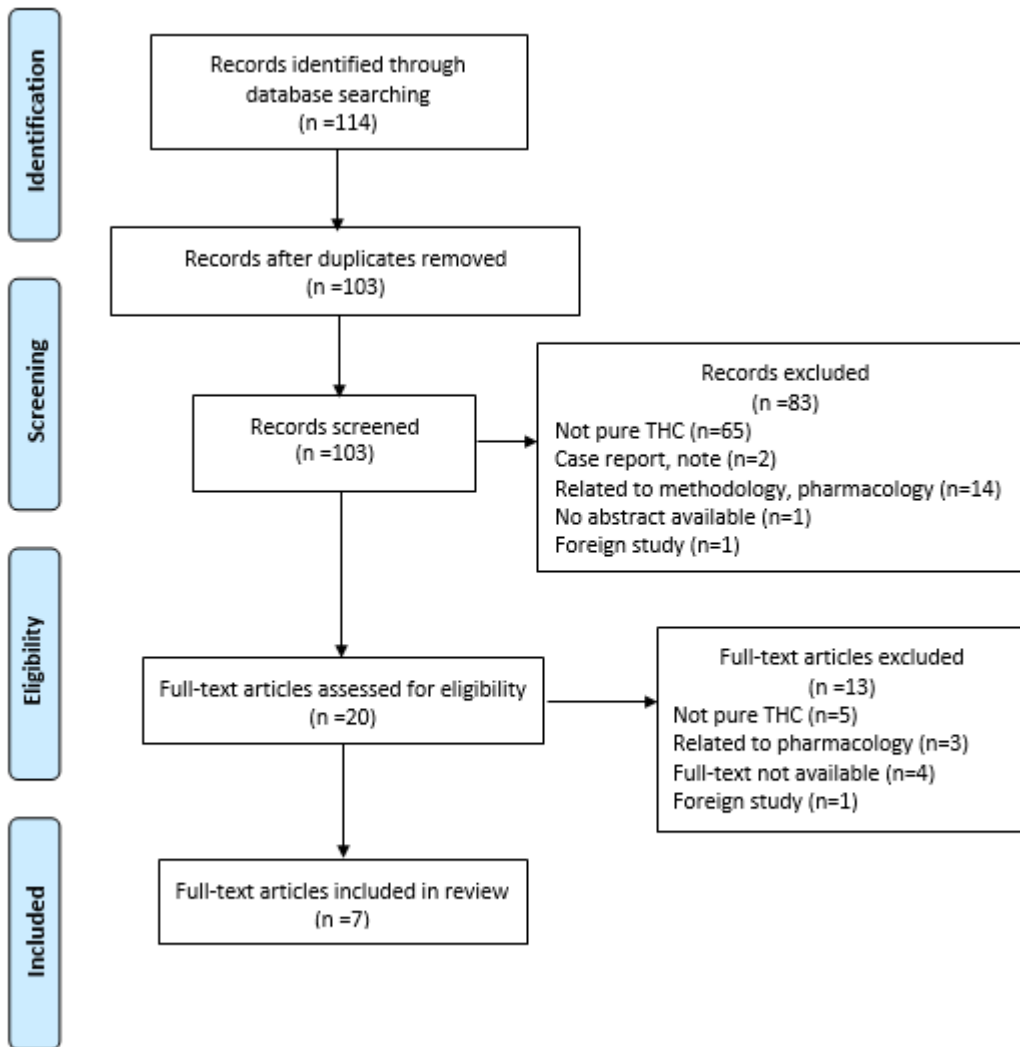
All full-text articles assessed for eligibility can be found on a separate Appendix file.

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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

delta-9-tetrahydrocannibinol

Annex 1: Member State Questionnaire

1. Introduction

Definition for the questionnaires used as the basis of this report:

Definition: Definition THC: Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised. This definition also includes the following stereochemical variant of THC: - dronabinol (Marinol; Syndros)

       a. Overview of Responses
          i. Q2

Q2: Please indicate your country.

86 representatives of 85 countries answered the questionnaire:

Algeria, Armenia, Australia, Austria, Bahrain, Barbados, Belarus, Belgium, Benin, Bhutan, Brazil, Brunei Darussalam, Bulgaria, Burundi, Cabo Verde, Canada, Colombia, Cote d'Ivoire, Cyprus, Czech Republic, Democratic Republic of the Congo, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Eritrea, Estonia, Ethiopia, Fiji, Finland, France, Gabon, Georgia, Germany, Greece, Honduras, Hungary, India, Indonesia, Ireland, Israel, Italy, Jamaica, Japan, Kenya, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Mali, Malta, Mauritius, Mexico, Micronesia, Monaco, Montenegro, Mozambique, Nauru, Netherlands, New Zealand, Nicaragua, Palau, Poland, Portugal, Republic of Korea, Republic of Moldova, Russian Federation, Saint Lucia, Serbia, Singapore, Solomon Islands, Spain, Sri Lanka, Sweden, Switzerland, Thailand, Tonga, Trinidad and Tobago, United Kingdom of Great Britain and Northern Ireland (the), United Republic of Tanzania, United States of America, Zambia, Zimbabwe.

          ii. **Q4**

Q4: Do you have any information about the use of **THC** for any purpose (including medical or non-medical use) in your country?

43 (50%) answered yes, 43 (50%) answered no.

2. Results: Approved medical use

    a. Medical use
        i. **Q5**
            1. Description of countries that have approved medical uses

Q5: At <u>national level</u>, is **THC** legally approved for **medical use** in your country? (including free text):

Countries with approved medical uses: Australia; Colombia; Denmark; Estonia; France (special license); Georgia; Germany; Israel; Italy; Malaysia; Malta; Mexico (currently in implementation); Netherlands; Portugal; Sweden (special license); Switzerland (special authorization necessary); United States of America.

        i. **Q6-Q16**

Q6: Please indicate any approved therapeutic indications for the medical use of **THC** in your country:

Disease condition	Number of countries	%
Epilepsy	2	9
Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury	4	27
Tourette's syndrome	2	18
Glaucoma	1	45
PTSD	1	36
Inflammatory bowel disease	1	0
Cancer	1	36
HIV/AIDS	2	18
Chronic pain	3	0
None specified	3	0
Other (often defined specific by product; for very specific conditions such as: anorexia associated with weight loss in patients with AIDS (US); or nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments (US, France); or specified as last choice treatment, if all other treatments failed)	6	0

None of the 12 countries indicated use for the following: Arthritis, dystonia, Huntington's disease, Parkinson's disease, anxiety, depression, schizophrenia/psychosis, Alzheimer's disease/ dementia, skin disease, irritable bowel syndrome, liver disease, obesity/diabetes, Crohn's disease, attention deficit disorder.

Q7: Please Indicate any symptoms that **THC** is approved to treat.

Symptom	Number of countries	%
Acute pain	1	9
Chronic non-cancer pain	3	27
Cancer pain	2	18
Nausea/ vomiting	5	45
Appetite stimulant	4	36
Headaches/ migraines	0	0
Muscle spasms	4	36
Seizures	2	18
Sleep problems	0	0
Alcohol withdrawal symptoms	0	0
Opioid withdrawal symptoms	0	0
Palliative care	1	9
Other	7	64
Total	11	

Countries answering were mainly from Europe (7) and the Americas (3); with 1 answer from Asia.

Q8. Please indicate whether there are any permitted marketed products of **THC**:

Sativex in 5 countries, and other THC/CBD combinations in 1 country; pure THC (dronabinol) in 5 countries; Israel has more than 70 applications

Q9: Are there any ongoing **approved clinical trials** in your country that are developing **THC** for medical use?

Germany, Israel and United States of America answered yes.

Q10: Please indicate product name/ trial number/ study phase of any ongoing trials that are developing products of **THC** for medical use.

United States of America: No product name. Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain, Sponsor: University of California, San Diego, Location: UC Center for Medicinal Cannabis Research, UC San Diego, San Diego, California, United States, Principle Investigator: Barth L Wilsey, MD, clinicaltrials.gov identifier: NCT02460642

United States of America: No product name. Title: Effects of Delta-9 Tetrahydrocannabinol (THC-dronabinol) on Retention of Memory for Fear Extinction Learning in PTSD: R61 Study, Sponsor: Wayne State University, Location: Eugene Applebaum College of Pharmacy and Health Sciences, Detroit,

Michigan, United States, Principle Investigator: Christine A. Rabinak, PhD, clinicaltrials.gov identifier: NCT03008005

United States of America: No product name. Title: The Safety, Tolerability and Efficacy of Dronabinol, for the Treatment of Nausea and Vomiting in Familial Dysautonomia, Sponsor: New York University School of Medicine, Principle Investigator: Horacio C Kaufmann, MD, Location: NYU Medical Center, New York, New York, United States, clinicaltrials.gov identifier: NCT02608931

Germany:Dronabinol; Eudra-CT: 2006-000439-85; Phase: 2
Germany:Dronabinol; Eudra-CT: 2007-001284-30; Phase: 1
Germany:Dronabinol; Eudra-CT: 2008-006881-27; Phase: 1
Germany:Dronabinol; Eudra-CT: 2018-000014-38; Phase: 2

Q11: Do individuals require a prescription to obtain **medical THC**?

All 12 countries who responded answered yes.

Q12. What types of professionals are allowed to <u>prescribe</u> **THC**?

10 of the 12 countries answered medical doctors/psychiatrists, 1 psychologists, and in 4 countries other professions.

Q13. What kinds of settings are approved to legally <u>dispense</u> **THC** in your country?

 Of the 12 countries answering, 9 allowed legal dispensing in pharmacies, 6 in hospitals, and 1 each in doctor's cabinets, outpatient clinics, palliative care facilities and others.

Q14: If patients use medical **THC** on prescription or recommendation of a health professional, will they be **reimbursed** for the costs of their medication?

In 4 of the 12 countries answering (33%), there is no reimbursement, in 2 (17%) there is reimbursement from the national health services, and in the rest of the countries there is mixed reimbursement (e.g., from some insurance companies, or only for approved indications, or reimbursement is currently under consideration).

Q15: Are any clinical guidelines used in your country for the prescribing of medical **THC**?

In 7 or 58% of the 12 countries answering, there are no guidelines, others have guidelines, guidance documents or Q & As.

Q16. Is there a regulatory agency in your country that monitors **THC** for medical use?

In all 12 countries answering, there are regulatory agencies to monitor THC for medical use. These are usually state regulatory agencies, but in Israel, there is a national Medical Cannabis Agency.

      b.   National legislation
            i.   Q17-21

Q17: How would you describe the trend in the number of users of **THC** for medical use over the last 3 years?

5 of the 12 countries answering (42%) indicated they did not know; 2 (17%) answered that medical THC remained at the same level, 2 (17%) indicated a substantial increase, and 2 (17%) indicated slight increase, and 1 (8%) indicated a decrease. All increases were in high-income countries.

Q18: In the past 3 years, has your country changed its national legislation around access to cannabis-related substances for **medical use**?

Of the 42 countries which answered, in 11 countries (26%), there had been changes in legislation for medical use of THC. These countries are in Europe (7), Latin America and the Caribbean (3), and Australasia (1).

Q19: If yes, what types of legislative changes has your country made for **medical use** of **THC**?

Legislative change	Number of countries	%
Change to the legal status of medical cannabis	6	40
Changes to the supply of medical cannabis (e.g. changes in licensing, import – or export of products)	6	40
Changes to access to medical cannabis (e.g. variety in products, therapeutic indications etc)	6	40
Other	8	53

Legislation changed mainly in the Americas (5 countries) and Europe (6 countries).

Q20: Is your country currently considering changes to its national legislation around access to **THC** for **medical use**?

Legislative changes prepared for THC	Number of countries	%
No	28	72
Yes	11	28
Total	39	100

Legislative changes are currently mainly prepared in Europe (6 countries); also two countries in the Americas, one in Australasia, one in Asia are preparing changes.

Q21: In your opinion, how do you feel **the changed legislation around access** to **THC** for medical use would impact / has impacted public health in your country?

Many of the countries who answered indicated not to know the impact of changed availability on public health (12 of 23 for decreased availability: 52%; 12 of 31 for increased availability: 39%).

As for decreased availability, 7 out of 23 countries (30%) saw a substantial or slightly negative impact, 3 (13%) expected no impact and 1 (4%) a slightly positive effect.

As for increased availability, 3 out of 31 countries (10%) saw a substantially positive impact, 9 (29%) a slightly positive impact, 3 (10%) expected no impact, 1 (3%) a slightly negative effect and 3 (10%) a substantially negative effect.

There were no distinct regional patterns, but most of the answering countries on these questions were from Europe or the Americas. As for positive answers, countries expected clinical use will reduce the burden of certain diseases.

3. Results: Prevalence of non-medical use

      a. Non-Medical use
            i. Q22

Q22: On a **national level**, are **THC** *legally* available for <u>non-medical use</u> in your country?

Only one out of 43 countries indicated legal availability of THC for non-medical use.

            ii. Q23

Q23: Are **THC** used for <u>cultural</u>, <u>ceremonial</u>, or <u>religious purposes</u> in your country?

Three countries out of 40 who answered (5%) indicated cultural, ceremonial or religious use, albeit this was considered in part illegal. From the answers it is not clear whether this is use of cannabis as a plant, of extracts and tinctures based on cannabis, or use of THC as defined in this report.

      b. Public health impact of use
          i. Prevalence data
              1. Adults:

Q24: Does your country collect prevalence data around the use of **THC**?

Seven out of 40 countries answering indicated to collect prevalence data on THC: Bulgaria; Dominican Republic; Ireland; Israel; Italy; Latvia; New Zealand.

Q25. Prevalence of use of **THC** amongst adults (over 18 years of age)?

Three countries (A,B,C) provided data but it is unclear whether these data do not pertain to cannabis in some of the countries that responded.

% of population used in lifetime: A) 8.3%, B) 33%, C) 9.8%
% of population used in the last year: A) 4.2%, B) 19%, C) 4.2%
% of population used in the past month: A) 2.6%, B) 13%, C) 1.6%
based on surveys from A) 2016 (age 19-64), B) 2016, C) 2015

              2. Youth:

Q26: Prevalence of use of **THC** for non-medical use amongst **young people** (below 18 years of age).

Two countries (A,B) provided data but it is unclear whether these data do not pertain to cannabis in some of the countries that responded.

% of population used in lifetime: A) 23.5%, B) 10%
% of population used in the last year: A) 11.2%
% of population used in the past month: A) 6.6%, B) 6%
based on surveys from A) 2016 (age 15-19), and B) 2014

1. General Trends:

Q27: How would you describe the number of users of **THC** for __non-medical use__ over the last 3 years in your country?

Of the 7 countries that responded, one reported a decrease, three reported no change, and 3 reported increases.

ii. Primary care presentations
    Q28-29

Q28: Does your country collect data about presentations to **primary care settings** due to the use of **THC**?

Of the 39 countries that responded, seven (18%) were unsure, and three (8%) indicated such a collection of data: Ireland; Italy; United Republic of Tanzania.

Q29: Number of __primary care__ presentations relating to **THC**.

No country presented data.

iii. Emergency presentations
    Q30-32

Q30: Does your country collect data about presentations to **emergency care settings** due to the use of **THC**?

Of the 38 countries reporting 11 (29%) were unsure, and 6 (16%) indicated such a collection of data: Bulgaria; Ireland; Italy; Malta; Mauritius; New Zealand; United Republic of Tanzania.

Q31: Number of individuals in the past year presenting to **emergency settings** relating to the use of **THC**.

Two countries provided data with 69 and 80 ER cases each for THC alone, and 33 and 170 for THC in combination with other substances. Data were from 2016) and 2017.

Q32: Please list the adverse effects presented for **THC** at the emergency room/department.

Four countries commented on reasons for presentations: injuries, Cannabis use disorders/withdrawal, and psychiatric comorbidity were each mentioned three times.

        iv.   Drug treatment presentations
              Q33-34

Q33: Does your country collect data about presentations to substance misuse treatment settings due to the use of **THC**?

Drug treatment for THC	Number of countries	%
No	23	59
Unsure	8	21
Yes	8	21
Total	39	100

Again, it is not sure, if these data do not pertain to cannabis in some of the countries answering

Q34: Number of individuals in the past year presenting to **substance misuse treatment** due to **THC:**

No clear answers.

        v.   Poison Centres
              Q35-Q36

Q35: Does your country collect data about calls to **poison control centres** due to the use of **THC**? and **Q36:** Number of calls to **poison control centres** due to the use of **THC.**

i. Poison Centres (Question 35, 36)

Poison centre visits due to THC	Number of countries	%
No	25	66
Unsure	6	16
Yes	7	18
Total	38	100

While THC is measured, the origin of the THC is not clear. Mostly this would be due to consumption of cannabis in other forms than pure THC

ii. Cases of impaired driving

Q37: Does your country collect data about cases of impaired driving due to the use of **THC**? And

Q38: Number of cases of **impaired driving** due to **THC:**

Impaired driving due to THC	Number of countries	%
No	21	55
Unsure	10	26
Yes	7	18
Total	38	100

While THC is measured, the origin of the THC is not clear. Mostly this would be due to consumption of cannabis in other forms than pure THC (comments on various questions to the questionnaire!)

c. National legislation

Q39: In the past 3 years, has your country changed its national legislation around access to **THC** for **non-medical use**?

While 3 of 38 countries claimed to have changed the law, detailed answers to question 39 and 40 would indicate, that these changes do not concern use of pure THC for non-medical use.

Q40: If yes, what types of legislative changes has your country made for **non-medical use** of **THC?**

See answer to Q39.

Q41: Is your country currently considering changes to its national legislation around access **THC** for **non-medical use**?

Three out of 36 countries indicated such potential changes; however, it is unclear, if they pertain to pure THC.

Q42: In your opinion, how do you feel the **changed legislation around access** to **THC** for non-medical use would impact / has already impacted public health in your country?

Potential impact on public health for these few countries with implemented and planned legislative changes cannot be ascertained.

4. Comments from countries

Most of the comments were about general legislation, and discussion of cannabis policy in general with few specific comments to pure THC and its role in present and future. Also, the role of medicinal cannabis was mentioned by several countries, given some applications from pharmaceutical companies to widen this role. Again, no specific comments on the medical use of pure THC. Finally, several countries highlighted that many questions referred to THC in general, and that it was not possible to separate between THC derived from using cannabis plants and resin versus THC stemming from 100% THC products such as medical products.

5. Conclusions

Overall, a limited number of countries have approved pure THC for medical use (17 of the 85 countries answering, mainly high-income countries in Europe and the Americas), but more countries are contemplating medical use of cannabis products including pure THC.

Answers to the questionnaire on prevalence and potential complications of pure THC are not conclusive and have to be taken very cautiously, as the comments of many countries indicated that they had been unsure about the questions, and/or that they had confounded medical or non-medical cannabis use in general with specific uses for pure THC as defined here (e.g., countries reported ESPAD (European School Survey on Alcohol and Other Drugs) results on prevalence, but this survey doesn't ask for pure THC; laws were mentioned which only deal with legalization or tolerance of cannabis, but not specifically with pure THC).

There should be clear monitoring efforts linked to increased medical approval pure THC, including effects on public health. While several countries expect such effects, they are unlikely given the current indications for pure THC products which are limited.