Health Canada Santé Canada

Information for Health Care Professionals

Marihuana (marijuana, cannabis)
dried plant for administration by ingestion or other means

Psychoactive agent

This document has been prepared for the Drug Strategy and Controlled Substances Programme to provide information on the use of marihuana for medical purposes. **Marihuana is not an approved therapeutic product and the provision of this information should not be interpreted as an endorsement of the use of this product, or marihuana generally, by Health Canada**.

Despite the similarity of format, it is not a Drug Product Monograph, which is a document which would be required if the product were to receive a Notice of Compliance authorizing its sale in Canada. This document is a summary of peer reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of marihuana. It is not meant to be comprehensive and should be used as a complement to other reliable sources of information.

This document should not be construed as expressing conclusions from Health Canada about the appropriate use of marihuana for medical purposes.

Marihuana (marijuana, cannabis) is not an approved therapeutic substance in Canada and no marihuana product has been issued a notice of compliance by Health Canada authorizing sale in Canada.

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Canada

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1.0 Chemistry

1.1 Starting material

Marihuana (Marijuana) is the common name for *Cannabis*, a hemp plant that grows throughout temperate and tropical climates in almost any soil condition. Delta-9-tetrahydrocannabinol (Δ^9-THC, referred to as THC) is the main psychoactive ingredient of cannabis. The flowering tops and leaves are used to produce cannabis for smoking . Marihuana is most commonly smoked in hand-rolled cigarettes ("joints") containing marihuana plant material.

1.2 Composition

1.2.1 Cannabinoids

Although the leaves and flowering tops of *Cannabis* plants yield more than 60 cannabinoids, the major active components are Δ^9-THC, cannabinol (CBN) and cannabidiol (CBD)[1]. Some reports mention the presence of delta-8-tetrahydrocannabinol (Δ^8-THC), equipotent to Δ^9-THC but the former may be formed by isomerization[2] during isolation. THC is the principal psychoactive ingredient of cannabis and the other components such as CBN, CBD and Δ^8-THC are present in smaller quantities and are not believed to make a significant contribution to the total effect of marihuana on behaviour or perception, but CBD may have other pharmacological effects[3]. THC is enantiomeric and only the (-) enantiomers occur in nature. The synthetic (+) positional enantiomers are not active. THC is sparingly soluble in water but has high lipid solubility[4]. An oral form of synthetic THC [(-) enantiomer], dronabinol (2.5, 5 or 10 mg, dissolved in sesame oil) in capsules is marketed in the US and Canada as Marinol®[5]. Structure-activity relationships, comprising the effects of alteration in the cannabinoid molecule, have been studied extensively and led to one synthetic drug, nabilone[6] being marketed as Cesamet®[7]. Nabilone in the product is a racemic mixture[8].

Cannabis also contains variable amounts of the carboxylic acid analogue of Δ^9-THC (tetrahydrocannabinolic acid, THCA). This substance readily degrades on heating

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[1]British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 7

[2] R Mechoulam, WA Devane, R Glaser. "Cannabinoid geometry and biological activity." In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999, part 1, chapter 1, pp 65-90.

[3] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p2.6.

[4] ER Garrett, CA Hunt. Physicochemical properties, solubility and protein binding of delta-9- THC. J Pharm Sci, 1974; 63: 1056-1064.

[5]Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[6] L Lemberger. Nabilone, a synthetic cannabinoid of medical utility. Chapter 46 In Marihuana and medicine, eds, GG Nahas, KM Sutin, D Harvey, S Agurell.,1999, pp561-566.

[7]Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[8] Souter RW. Anal Profiles Drug Subs, 181, 10: 499-512.

and smoking to yield THC [9],[10]. The total of the THC and its corresponding acids is almost always considered in potency content, according to Agurell *et al*[11].

1.2.2. Quantitation of cannabinoids.
This section describes the amounts of major cannabinoids found in plant material and is divided into legal sources and "street" or clandestine sources.

1.2.2.1 Legal sources
The best described official legal marihuana is from the US. NIH, by contract from the National Institute of Drug Abuse (NIDA) who subcontracts to the Research Triangle Institute to serve as a central facility for the manufacture and distribution of standardized marihuana cigarettes and cannabinoid preparations for research purposes[12]. The plants, grown by the University of Mississipi are gathered in 100kg batches, dried and partly stripped of large stems, before being sent for further processing. At this point there is analysis for THC, CBN and CBD towards selective blending of the batches to control the final THC potency of the cigarettes. The processed blended plant material is made into cigarettes about 8.5 mm in diameter and 85 mm long. There is careful quality control during the manufacture to produce a consistent product, including particle size, weight, dimensions, moisture content, as well as cannabinoid content.

Health Canada has contracted Prairie Plant Systems to produce cannabis for research. Details regarding the composition of this material are available and may be obtained from Health Canada.

1.2.2.2 " Street" recreational marihuana
Because the regulations allow patients to grow their own cannabis which would not be standardized, it is useful to record the cannabinoid content of "street" or seized marihuana. Agurell *et al* [13] noted that THC is present in concentrations of from 0.3 to 3% in plant material, but Ameri[14] wrote in 1999 that the average THC content of confiscated marihuana was 0.35% in 1974 and had risen to 3.54 % in 1990. There is more recent evidence that plant breeding programs in the

[9] PB Baker, KR Bagon, TA Gough. Variation in the THC content in illicitly imported Cannabis products. Bull Narc, 1980; 32: 47-54.

[10] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000, p. 37

[11] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[12]Thomas BF, Parker VL, Caddell LW, Jones LV, Sabharwal SK, McDaniel AI, Keimowitz AR, Scheffler NM, Hart ED, Mitchell JM, Davis KH. Composition of a standard marihuana cigarette. Chapter 6 In Marihuana and medicine, eds, GG Nahas, KM Sutin, D Harvey, S Agurell.,1999, pp137-143

[13] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

[14] A Ameri. The effects of cannabinoids on the brain. Progress in neurobiology, 1999; 58: 315-348

Netherlands and California are producing new varieties that have much higher concentrations of THC [15].

In discussions with the Canadian Senate Special Committee on Illegal Drugs, RCMP narcotics experts in British Columbia emphasized that it is difficult in the current state of affairs to determine the average THC/THCA content of cannabis in the country or in a given province, in particular as a result of the extreme variability both of seized material and methods of analysis. The officers who seize suspected material are not required to preserve samples in a standard procedure, so it may lose some of its THC content[16]. Some stability concerns are discussed in section 1.3 below.

Information from"street" sample seizures of marihuana in Canada over a period roughly from April 2000 to April 2002[17], found a mean %THC of about 10% (range 3-30%), excluding poor quality marihuana such as that with THC contents of 0-3% (22% of all samples). [It should be noted that the samples were not randomly selected]. Clearly the range of amounts of THC in a "joint", which also is variable in weight, leads to a wide range of available doses, considered later, under section 3.0. (According to the World Health Organization[18], a typical joint contains between 0.5 and 1.0 g of cannabis plant matter, average 750 mg.)

1.2.3 Other ingredients

There are other components in marihuana joints which are common to tobacco and the smoke from them is considered chemically similar to that from tobacco cigarettes[19, 20]. However, some investigators report that two potent carcinogens in tobacco smoke, benzanthracene and benzpyrene, are present in higher amounts in marihuana smoke[21]. Differences in the smoking techniques used by marihuana and tobacco smokers are reported to result in three fold higher levels of tar and five-fold higher levels of carbon monoxide being retained in the lungs during cannabis than during tobacco smoking [22]. This greater retention of tar and carbon monoxide from cannabis smoke may offset the fact that a marihuana smoker typically smokes fewer

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[15] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p5

[16] Report of the Senate Special Committee on Illegal Drugs 2002, Vol I, Part II, p 7, Canadian Parliament, Senate, Ottawa

[17] Personal Communication, Drug Strategy and Controlled Substances Programme, Health Canada, September 2002

[18] World Health Organization. Cannabis: a health perspective and research agenda, 1997 http://www.who.int/substance_abuse/docs/cannabis.pdf

[19] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p 191.

[20] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 14

[21] M Novotny, ML Lee KD Bartle. A possible chemical basis for the higher mutagenicity of marijuana smoke as compared to tobacco smoke. Experientia 1976, Mar 15;32: 280-282.

[22] T-C Wu, DP Tashkin, B. Djahed, JE Rose. Pulmonary hazards of smoking marihuana as compared to tobacco. New Eng J Med, 1988; 318: 347-351.

cigarettes per day than a tobacco smoker (i.e., the exposure to tar and carbon monoxide could be similar for both groups of smokers)[23,24].

Historically, marihuana as medicine was formulated as an alcoholic tincture and many early clinical observations were based on such formulations[25]. Plant-based foodstuffs and drinks for oral ingestion are described by Iversen[26]. These usually involve heating, which converts THC from THCA. He reports that a common method of preparation is to mix the plant leaf material in cooking oil, butter or margarine and after heating, then to strain out the plant debris and use the oily extract for cooking to make cakes or biscuits ("brownies"). There is no information on the strengths of these preparations. However, this method of use avoids the hazards of smoke to the lungs,

The synthetic THC, dronabinol (Marinol®), is marketed dissolved in sesame oil, with anti-oxidants contained in soft gelatin capsules with 2.5, 5 and 10 mg strengths [27].

1.3 Stability and storage

Most of the information on stability of marihuana is from the 1970's and 1980's and does not distinguish between THC and THCA. The latter is degraded to THC by pyrolysis during smoking or in the inlet of gas chromatographs used in forensic analysis[28]. Heat, light, humidity, acidity and oxidation all affect the stability of cannabis[29, 30]. One of the analytical concerns is degradation of sample at room temperature with THC degrading to CBN, possibly from enzymes present in the plant material. The temperature and humidity are possibly critical in retarding loss of THC in recently harvested plant material[31]. Historic samples of cannabis showed low concentrations of THC, with most of their cannabinoid content being the less active CBN, the main chemical degradation product of THC[32]. One study indicated that cannabis in solution is unstable to light, but plant material is more susceptible to oxidation leading to decrease of THC with increase

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[23] RC Peterson. Importance of inhalation patterns in determining the effects of marijuana use. Lancet, 1979 (I): 727-728.

[24] DP Tashkin, AH Coulson, VA Clark, M Simmons, LB Bourque, S Duann, GH Spivey, H Gong. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis, 1987;135: 209-216.

[25] A Mack, J Joy "Marihuana as medicine: the science beyond the controversy." National Academy Press, Washington D.C. 2001, p 13-19

[26] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000, p 17.

[27] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[28] PB Baker, BJ Taylor, TA Gough. The tetrahydrocannabinol and tetrahydrocannabinolic acid content of cannabis products. J Pharm Pharmacol, 1981; 33: 369-372.

[29] ER Garrett, CA Hunt. Physicochemical properties, solubility and protein binding of delta-9- THC. J Pharm Sci, 1974; 63: 1056-1064.

[30] R Mechoulam. Chemistry of cannabis. Handbook Exp Pharmacol, 1981; 55: 119-134.

[31] K Narayanaswami, HC Golani, HL Bami, RD Dau. Stability of Cannabis sativa L. samples and their extracts, on prolonged storage in Delhi. Bull Narc, 1978; 30: 57-69.

[32] DJ Harvey, Stability of cannabinoids in the dried samples of cannabis from around 1896-1905. J. Ethnopharmacol, 1990; 28: 117-118.

of CBN[33], although the latter does not appear to be the only product[34]. The available information suggests that THC in recently harvested plant material stored in the dark in dry, tightly- closed containers, in a refrigerator would be stable for several months. NIDA reports[35] that retention samples of their carefully prepared and standardized cigarettes are stable for months, particularly when stored below 0°C . However, even at 18°C, there is only a loss of a third of the THC potency (2.87 to 1.8% THC) over 5 years, with some increase of CBN.

1.4 Characteristics of marihuana smoking

Marihuana is probably most commonly smoked in hand-rolled joints in which marihuana resin or leaf is combined with tobacco. Marihuana is also smoked in pure form in joints, pipes or other devices[36].

A useful summary of the similarities and differences in tobacco and marihuana smoking is given by the following excerpt from the U.K. Royal College of Physicians submission to the UK House of Lords, Select Committee[37]:

> "Compared to tobacco smoking the following differences in smoking pattern, and consequences or relevance to health, apply to marihuana:
>
> - The number of joints smoked per day is usually substantially less than the number of cigarettes smoked by a pure tobacco smoker. The total amount of smoke inhaled is therefore less with marihuana.
> - The absence of filters in the smoking devices means that a higher proportion of tar (the constituents of which are very similar to tobacco tar, except that marihuana smoke does not contain nicotine) is inhaled.
> - Smoke from joints or other sources tends to be inhaled more deeply, and held in the lungs for longer, than pure tobacco smoke, so deposition of combustion products in the lung is proportionately greater.
> - Some marihuana smokers attempt to increase drug absorption by performing a valsalva manoeuvre after deep inhalation, which may lead to local barotrauma in the lung[38].

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[33] JW Fairbairn, JA Liebmann, JA Rowan.The stability of cannabis and its preparations on storage. J Pharm Pharmacol, 1976; 28: 1-7.

[34] GS Lewis, CE Turner. Constituents of Cannabis sativa L. XIII: Stability of dosage form prepared by impregnating synthetic delta-9-trans-tetrahydrocannabinol on placebo Cannabis plant material. J Pharm Sci, 1978; 67:876-878.

[35] Thomas BF, Parker VL, Caddell LW, Jones LV, Sabharwal SK, McDaniel AI, Keimowitz AR, Scheffler NM, Hart ED, Mitchell JM, Davis KH. Composition of a standard marihuana cigarette. Chapter 6 In Marihuana and medicine, eds, GG Nahas, KM Sutin, D Harvey, S Agurell.,1999, pp137-143

[36] CH Ashton. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry, 2001; 178:101-106.

[37] House of Lords, Select Committee on Home Affairs, Memorandum 59, March 2001 U.K. John Brittain for Royal College of Physicians website UK parliament.

[38] MK Johnson, RP Smith, D Morrison, G Laszlo, RJ White. Large lung bullae in marijuana smokers. *Thorax* 2000;55:340-2.

As a result, the potentially lower health hazard (relative to tobacco smoking) of a lower frequency of marihuana smoking is offset to a substantial degree by differences in inhalation practice and the lack of filtration. Marihuana smoke is also hotter than tobacco smoke, which is also more damaging."

2.0 Clinical Pharmacology

2.1 Pharmacodynamics

This section will describe mainly acute effects of marihuana, while section 4 will be concerned with possible therapeutic benefits and section 8 with risks of adverse effects of chronic use.

The literature on the pharmacologic effects of marihuana is diverse and many early studies suggesting that it is a highly dangerous drug have been refuted or shown to be spurious [39]. The IOM report attempted to put this in a balanced context[40]: "Marihuana is not a completely benign substance. However, except for the harms associated with smoking, the adverse effects of marihuana use are within the range tolerated with other medicines."

Most of the pharmacodynamic information on marihuana in humans refers to the effects of the major constituent THC. CBD does not appear to have psychoactivity and its major effect appears to be interference with drug metabolism in the liver, including THC metabolism, by inhibition of cytochrome P_{450} enzymes. However, in rats, CBD was shown to have an anticonvulsant action somewhat between phenytoin and ethosuximide[41]. CBN, while only weakly active compared to THC in brain, appears to have activity in isolated immune cells[42].

THC has complex effects on the central nervous system, including central sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissue and research on their physiological role may lead to better understanding the mechanism of activity of THC and other cannabinoids[43]. Two types of cannabinoid receptors, CB1 and CB2, have been identified. CB1, the most abundant, is distributed in brain in discrete areas including those concerned with motor activity and postural control (basal ganglia, cerebellum), memory and cognition (cerebral cortex and hippocampus) emotion

[39] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p178.
[40] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p3.49
[41] SA Turkanis, KA Smiley, HK Borys, DM Olsen, R Karler. An electrophysiological analysis of the anticonvulsant action of cannabidiol on limbic seizures in conscious rats. Epilepsia 1979 Aug;20(4):351-63.
[42] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 2.5
[43] RG Pertwee. Cannabis and cannabinoids: pharmacology and rationale for clinical use. Forsch. Komplementarmed, 1999; 6 Suppl 3: 12-15.

(amygdale and hippocampus) and sensory perception (thalamus)[44]. The endogenous substance anandamide (arachidonoyl-ethanolamine) appears to be the agonist for the CB1 receptor and is found with the receptor in the neuronal membranes. A second endogenous agonist, 2-arachidonoyl-glycerol (2-AG), has lower potency, but is more abundant[45]. More recent research, however, suggests that 2-AG is the natural ligand for both the CB1 and the CB2 receptors and both receptors are primarily 2-AG receptors with evidence mounting that 2-AG is a physiologically essential molecule[46,47]. The second cannabinoid receptor, CB2 , is most abundant in spleen macrophages and cells of the immune system[48]. CBN shows great affinity for this receptor, which may be relevant for the effects of marihuana on the immune system[49].

While not involved itself in interneuronal communication, this system for which THC is a partial agonist, appears to modulate the excitability and responsiveness of neurons by interactions with cyclic AMP in the intracellular post-receptor communication system. This occurs in many different types of neurons including cholinergic, noradrenergic, dopaminergic and serotonin pathways[50]. The mechanism of action and physiological function of this endogenous cannabinoid system are currently under investigation.

The table below, adapted from the BMA Report[51], does note some of the effects of cannabis. Many of the effects are biphasic, e.g., increased activity with acute or smaller doses, decreased activity with larger doses or chronic use. Effects differ greatly among individuals and may be greater in severely ill and elderly patients.

Table 1. Some pharmacological actions of cannabis in man

Body System/effect	Detail of effects
CNS psychological	Euphoria ("high"), dysphoria, anxiety, depersonalization, precipitation or aggravation of psychosis
Perception	Heightened sensory perception, distortion of space and time, sense, hallucinations, misperceptions.
Sedative	Generalised CNS depression, drowsiness, somnolence; additive

[44] M Herkenham, AB Lynn, MR Johnson, LS Melvin, BR de Costa, KC Rice. Characterization and localization of cannabinoid receptors in rat brain: a quantitative *in vitro* autoradiographic study. J Neurosci. 1991; 11:563-583.
[45] RG Pertwee, RA Ross. Cannabinoid receptors and their ligands. Prostaglandins Leukot Essent Fatty Acids, 2002; 66:101-121
[46] T.Sugiura, K Waku. 2-Arachidonoylglycerol and the cannabinoid receptors. Chem Phys Lipids. 2000;108:89-106.
[47] Sugiura T, K Waku. Cannabinoid receptors and their endogenous ligands.J Biochem (Tokyo). 2002 132: 7-12.
[48] CC Felder, M Glass. Cannabinoid receptors and their endogenous agonists. Ann Rev Pharmacol Toxicol. 1998;38:179-200.
[49] S Munro, KL Thomas, M Abu-Shaar. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993; 365: 61-65.
[50] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 pp52-65
[51] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 19

Body System/effect	Detail of effects
	with other CNS depressants.
Cognition, psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance especially in complex demanding tasks.
Motor function	Increased motor activity followed by inertia and in coordination, ataxia, dysarthria, tremulousness, weakness, muscle twitching.
Analgesic	Currently available oral cannabinoids are similar in potency to codeine (but from a different mechanism).
Anti-emetic, increased appetite	With acute doses; effect reversed with larger doses or chronic use (tolerance).
Tolerance	To most behavioural and somatic effects, including the "high".
Dependence, abstinence syndrome	Has been produced experimentally following prolonged intoxication: symptoms include disturbed sleep, decreased appetite, restlessness, irritability and sweating. Information from therapeutic use lacking.
Cardiovascular system Heart rate	Tachycardia with acute dosage; bradycardia with chronic use.
Peripheral circulation	Vasodilation, conjunctival redness, postural hypotension.
Cardiac output	Increased output and myocardial oxygen demand
Cerebral blood flow	Increased with acute dose, decreased with chronic use.
Respiratory system Ventilation	Small doses stimulate, larger doses depress.
Bronchodilation	Coughing, but tolerance develops.
Airways obstruction	From chronic smoking.
Eye	Decreased intraocular pressure.
Immune system	Chronic use: impaired bactericidal activity of macrophages in lung and spleen.
Reproductive system Males	Antiandrogenic, decreased sperm count and sperm motility (chronic use, but tolerance may develop).
Females	Suppression of ovulation, complex effects on prolactin secretion. On chronic use, increased obstetric risk.

Most recent reviews[52, 53, 54, 55] separate the effects of smoking and the potential adverse effects of cannabis by other routes, although some of the potential consequences of

[52] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999

[53] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997.

[54] Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, 1999.

[55] The health effects of cannabis, eds H Kalant, W Corrigall, W. Hall. R Smart, Centre for Addiction and Mental Health, Toronto, 1999.

smoking are extrapolated from tobacco smoking. It is also difficult to differentiate the effects of the extremely variable product "cannabis" from those of plant-based or synthetic THC (Marinol®). Certainly most of the quantitative results in humans have been obtained with THC and not the other cannabinoids.

The acute effects of smoking marihuana involve the almost immediate euphoria (the marihuana "high"), cardiovascular, bronchopulmonary, ocular, psychological and psychomotor effects. Maximum effects from the "high" occur within 15 minutes or sooner after smoking and the psychological effects reach a plateau which can last for several hours. However, on first dosing, some people experience dysphoria and anxiety. The effects on the cardiovascular system (tachycardia etc.) decline much faster as THC is distributed out of the circulatory system. It is noted that cardiac acceleration is the most consistent of the physiological effects of marihuana[56, 57].

The major immediate difference in the effect of smoking compared to oral administration is a bronchodilator effect rapidly peaking at 15-20 minutes and persisting for 20 minutes after smoking[58]. Irritation of the eyes with redness has also been mentioned to coincide with THC plasma peak.[59] This rapid peak and short duration of activity contrasts with oral administration. THC (dronabinol, Marinol®) has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect may continue for 24 hours or longer after administration[60].

The short-term psychoactive effects of marihuana smoking include euphoria, relaxation, time- distortion, perception of enhanced sensory experiences (such as music) and loss of inhibitions that may result in laughter [61]. This is followed by a depressant period [62]. While there is some inconsistency in reports of the acute effects on memory and motor- skills that may relate to the experience of the subject [63 ,64,65], most reviews note that marihuana use is associated with impaired function of a variety of cognitive tasks and short-term

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[56] P Beaconsfield, J Ginsburg, R Rainsbury. Marihuana smoking. Cardiovascular effects in man and possible mechanisms. N Engl J Med. 1972; 287: 209-212.

[57] M Perez-Reyes. Marijuana smoking: factors that influence the bioavailability of tetrahydrocannabinol. NIDA Res Monogr. 1990; 99: 42-62.

[58] DP Tashkin in "The health effects of cannabis", eds H Kalant, W Corrigall, W. Hall. R Smart, 1999. ref 71, p 315.

[59] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

[60] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[61] W Hall, N Solowij.Adverse effects of cannabis. Lancet. 1998;352: 1611-6.

[62] A Ameri. The effects of cannabinoids on the brain. Prog Neurobiol. 1999; 58:315-348.

[63] RV Fant, SJ Heishman, EB Bunker, WB Pickworth.Acute and residual effects of marijuana in humans. Pharmacol Biochem Behav. 1998;60: 777-784.

[64] TH Kelly, RW Foltin, MW Fischman. Effects of smoked marijuana on heart rate, drug ratings and task performance by humans. Behav Pharmacol.1993; 4: 167-178.

[65] GBarnett, V Licko, T Thompson. Behavioral pharmacokinetics of marijuana. Psychopharmacology (Berl). 1985; 85: 51-56.

memory[66 67,68,69.] A major concern from such an acute effect is impairment for driving or operating intricate machinery[70,71,72]. There are reports of reduced skills on flight simulators by experienced pilots 24 h after smoking one marihuana cigarette[73]. Plasma THC levels attained after smoking seem to have a dose and concentration dependent effect on cognitive tasks[74] .

2.2 Pharmacokinetics

This section will be restricted to human pharmacokinetics, mainly of smoked cannabis, but with some comparisons to oral THC including dronabinol (Marinol®).

2.2.1 Absorption:

2.2.1.1 Smoked Cannabis:

The estimation of dose administered by the smoking route is a major variable in the assessment of absorption of cannabinoids (mainly THC) in humans. The source of the plant material and the composition of the cigarette, together with the efficiency of smoking by the subject are additional uncontrolled factors. As noted in the chemistry section, it might be reasonable to consider about 10% (range 3-30%) as an average for THC in Canadian marihuana.

Regarding smoking techniques, one research group remarked that "it is incredible to see the variety of techniques marihuana users employ to smoke their cigarette"[75]. It appears that habitual (heavy) marihuana smokers can increase the amount absorbed and this is attributed to more efficient smoking technique[76].

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[66] A Ameri.The effects of cannabinoids on the brain. Progress in neurobiology, 1999; 58: 315-348

[67] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 2.27

[68] Hollister LE. Health aspects of cannabis: revisited. Int J Neuropsychopharmacol. 1998; 1: 71-80.

[69] LL Miller "Acute effects on human memory", in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, Ch 15. pp 227-231.

[70] RW Hansteen, RD Miller, L Lonero, LD Reid, B Jones "Effects of cannabis and alcohol on automobile driving and psychomotor tracking." Annals of the New York Academy of Science, 1976; 282: 240-256.

[71] A Smiley. Marijuana: On-road and driving-simulator studies, in "Health effects of cannabis", H Kalant, W Corrigall, W hall, R Smart (eds), Centre for Addiction and mental Health, Toronto, 1999, pp173-179.

[72] CJ O'Kane, DC Tutt, LA Bauer. Cannabis and driving: a new perspective.Emerg Med (Fremantle) 2002;14: 296-303.

[73] VO Leirer, JA Yesavage, DG, Morrow. Marijuana carry-over effects on aircraft pilot performance. Aviat Space Environ Med. 1991; 62: 221-227.

[74] Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. Pharmacol Biochem Behav. 1990 Nov; 37(3):561-565.

[75] M Huestis " Pharmacokinetics of THC in inhaled and oral preparations". In Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999. pp 105-116.

[76] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

Table 2 indicates some of the variation found by various workers who investigated the amounts lost during smoking, with 69% regarded as the maximum available for absorption *via* mainstream smoke from a smoking machine.

Table 2: Estimates of percent of THC flow during smoking

Sidestream	Pyrolyzed	Mainstream	Butt	Ref.
		20		Agurell *et al* [79] Ohlsson *et al* [80]
6-53	31-50	16-69*	10-21	Huestis [83]
40-50	23-30	20-37		Perez-Reyes [77]

* High from single puff smoking machine [78] .

However, as much as half the active drug in cigarettes can be lost to pyrolysis. In one experiment in which cigarettes containing about 19 mg of THC were smoked it was reported that an average of 82% of the THC in the marihuana cigarette did not appear in the systemic circulation. An average of 6 mg (31%) was retained in the cigarette butts, with other losses due to pyrolysis and side-stream smoke during smoking [79] [80]. However, when the butt was smoked it was estimated that 50% of the total THC dose is delivered[81]. In experiments using a smoking machine, 16-19% of the THC was found in mainstream smoke, but when the cigarette was smoked in a single puff, avoiding side stream smoke, 69% of the THC was in mainstream smoke: about 30% of THC thus appears to be destroyed by pyrolysis[82]. The NIDA group[83] summarize that 20 to 37% of the THC is delivered in mainstream smoke, with pyrolytic destruction of 23 to 30% and sidestream losses of 40 to 50% of the dose. Less is known about the fate of

[77] M Perez-Reyes. Marijuana smoking: factors that influence the bioavailability of tetrahydrocannabinol. NIDA Res Monogr. 1990; 99: 42-62.

[78] KH Davis, IA McDaniel, LW Cadell, PL Moody. Some smoking characteristics of marijuana cigarettes. In: S Agurell, WL Dewey, RE Willette, eds. The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects. New York: Academic press, 1984.pp97-107

[79] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

[80] A Ohlsson, JE Lindgren, A Wahlen, S Agurell, LE Hollister, HK Gillespie. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking.. Clin Pharmacol Ther. 1980; 28: 409-416.

[81] Truitt EB Jr. Biological disposition of tetrahydrocannabinols. Pharmacol Rev. 1971; 23: 273-8.

[82] KH Davis jr., IA McDaniel, Jr., LW Caldwell, P Moody. "Some smoking characteristics of marijuana cigarettes" in The Cannabinoids: Chemical, pharmacologic and therapeutic aspects, eds S Agurell, WL Dewey, RE Willette, Academic Press, N.Y., 1984, pp 97-109.

[83] MA Huestis, AH Sampson, BJ Holicky, JE Henningfield, EJ Cone. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther. 1992 ; 52: 31-41.

smoked CBD and CBN, but it appears that the results [84] are similar to THC, except that CBN plasma levels appear to be about twice as variable as other cannabinoids.

THC absorption by inhalation is extremely rapid and is the main reason why this route of dosing is preferred by many people[85] with a bioavailability of 18 to 50% from the cigarette[86]. From experiments with deuterium labelled THC given intravenously (5 mg) or smoked in cigarettes (10mg) heavy smokers (n=14) overall were found to obtain higher biovailability (23-27%) of THC than light (n=13) marihuana smokers (10 to 14% respectively)[87],[88]. In the two experiments there was high between subject variability (CV 40-70%) with overlap between groups. A mean bioavailability of 20% with range of 10 to 30% for THC is given by Iversen [89].

Standardised cigarettes have been developed by NIDA and the relationships among cannabis (THC) content, dose administered and resultant plasma levels has been investigated. Smoking cannabis containing1.64% THC (mean dose13.0 mg THC), resulted in mean peak THC plasma levels of 77 ng/ml.[90]

A comparison of cannabis "joint" potency and resulting plasma THC concentrations from carefully controlled smoking experiments is shown in table 3.

[84] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

[85] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p46-47.

[86] M Huestis " Pharmacokinetics of THC in inhaled and oral preparations" in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, 1999. pp 105-116.

[87] JE Lindgren, A Ohlsson, S Agurell, L Hollister, H Gillespie. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. Psychopharmacology (Berl) 1981;74(3):208-12

[88] A Ohlsson, JE Lindgren, A Wahlen, S Agurell, LE Hollister, HK Gillespie. Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. Biomed Mass Spectrom 1982 Jan;9(1):6-10

[89] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p 47

[90] A Ohlsson, JE Lindgren, A Wahlen, S Agurell, LE Hollister, HK Gillespie. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980; 28: 409-416.

Table 3. Relationship between cannabis potency and peak THC plasma concentrations (ng/ml)[91], including ± standard deviation and range.

THC content in cannabis	No. of subjects	Plasma THC (ng/mL) ± s.d.	THC range (ng/mL)
1.00%	6	90.4 ± 20.2	45.6 – 187.8
1.32%	6	100.0 ± 10.1	62.8 – 125.3
1.97%	6	119.8 ± 10.6	44.5 – 180.9
2.40%	18	63.0 ± 8.6	11.7 – 137.0
2.54%	6	162.6 ± 18.7	107.4 – 204.7
4.84%	12	124.2 ± 16.2	44.8 – 218.0

Even in these controlled experiments there is clearly great variation in the amount absorbed among individuals and a poor relationship between amount of THC in cigarettes (1 to 4.8%) and peak plasma THC concentrations.

Arguably the most reliable information on absorption of marihuana is from work from Huestis et al.[92], where a strict smoking protocol and an extremely rapid blood sampling technique were applied in six volunteers with cigarettes at two dose levels containing 1.75% and 3.55% THC. Concentrations of THC were detected in 2 minutes, just after the first puff and peak concentrations occurred at 9 minutes, just before the last puff (which began at 9.8 minutes). Average peak plasma concentrations of 79 ± 25.2 and 152 ± 86.3 ng/ml respectively, were obtained for the cigarettes containing 1.75 and 3.55% THC. Despite a rigorous smoking protocol, the variation displayed from the higher dose was from about 80 to 260 ng/ml. Although the reported average maximum concentration occurred at 9 minutes, just before the final puff, the investigators noted that the time to peak is influenced by the number of puffs, time between puffs, and the volume and length of inhalations. This was clear from other detailed studies [93],[94]. However, the effectiveness of breath-holding with 3.55% THC potency cigarettes appears to be limited. After puffing the cigarette, a 20 second hold did not increase the plasma concentrations significantly over a 10 second hold [95].

There is little pharmacokinetic information for THC and other cannabinoids comparing gender. In a study with tritiated THC administered intravenously and

[91] M Perez-Reyes. Marijuana smoking: factors that influence the bioavailability of tetrahydro-cannabinol. NIDA Res Monogr. 1990;99:42-62

[92] MA Huestis, AH Sampson, BJ Holicky, JE Henningfield, EJ Cone. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther. 1992 ; 52: 31-41,

[93] M Perez-Reyes. Marijuana smoking: factors that influence the bioavailability of tetrahydro-cannabinol. NIDA Res Monogr. 1990;99:42-62

[94] JL Azorlosa, SJ Heishman, ML Stitzer, JM Mahaffey. Marijuana smoking: effect of varying delta 9-tetrahydrocannabinol content and number of puffs. J Pharmacol Exp Ther. 1992; 261:114-122

[95] JL Azorlosa, MK Greenwald, ML Stitzer. Marijuana smoking: effects of varying puff volume and breathhold duration. J Pharmacol Exp Ther. 1995; 272: 560-569.

orally to six young men and women no differences in pharmacokinetics, including disposition and metabolism were noted[96]. In another small study, three men and three women who were experienced marihuana smokers smoked two 1% THC cigarettes with a two hour interval between doses. They were asked to smoke at their usual rate. There was a gender difference in the smoking rate with males smoking more rapidly with more puffs (28 *vs*. 11 for the women). There was a tendency for peak concentrations to be lower for the women, but there was no significant difference in AUC[97,98].

THC levels in plasma decreased rapidly after cessation of smoking and were below 5 ng/ml, 2 hours after smoking; mean concentrations declined by about 50%, 15 minutes after[99] reaching the maximum[100] . However, THC from a single dose can be detected in plasma for at least a day using modern sensitive analytical techniques and for 13 days in chronic users[101]. The decline of THC in plasma is multiphasic and as Harvey[102] notes, the estimates of the terminal half-life of THC in humans have increased as analytical methods have become more sensitive. There is still no consensus. It is probably safe to say that the terminal half-life of THC averages at least a week and could be considerably longer. The half-life in plasma does not appear to be different between heavy and light users[103].

2.2.1.2 Oral THC

THC is almost completely absorbed (90 to 95%) after single oral doses according to recovery of ^{14}C-labeled dose[104]. From an oral dose of 20 mg THC in a chocolate cookie, compared to intravenous infusion of 5 mg, the systemic availability was

[96] ME,Wall, BM Sadler, D Brine, H Taylor, M Perez-Reyes. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther. 1983; 34: 352-63.

[97] M Perez-Reyes, SM Owens, S Di Guiseppi.The clinical pharmacology and dynamics of marihuana cigarette smoking. Clin Pharmacol 1981; 21: 201S-207S

[98] G Barnett, CW Chiang, M Perez-Reyes, SM Owens. Kinetic study of smoking marijuana. J Pharmacokinet Biopharm. 1982 ; 10: 495-506.

[99] MA Huestis, AH Sampson, BJ Holicky, JE Henningfield, EJ Cone. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther. 1992 ; 52: 31-41.

[100] M Huestis " Pharmacokinetics of THC in inhaled and oral preparations" in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, 1999. pp 105-116.

[101] E Johansson, S Agurell, LE Hollister, MM Halldin. Prolonged apparent half-life of delta 1-tetrahydrocannabinol in plasma of chronic marijuana users. J Pharm Pharmacol. 1988;40: 374-375..

[102] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999, pp 91-103.

[103] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[104] L Lemberger, JL Weiss, AM Watanabe, IM Galanter, RJ Wyatt, PV Cardon. Delta-9-tetrahydrocannabinol. Temporal correlation of the psychologic effects and blood levels after various routes of administration. N Engl J Med. 1972; 286: 685-688.

only 4 to 12%[105] and is described as being slowly and unreliably absorbed [106]. While most subjects had peak plasma THC concentrations between 1 to 2 hours, some of the 11 subjects only peaked at 6 hours and many had more than one peak. When tritiated THC was administered (total doses of 15 mg in women and 20 mg in men) in oil enclosed in capsules, 10 to 20% of the administered dose reached the systemic circulation. The peak THC concentrations observed were in the range 10 to15 ng/ml, about one tenth as levels attained by efficient smoking [107]. Only 10-20% of synthetic THC (dronabinol) administered in capsules with sesame oil, enters the systemic circulation indicating extensive first- pass metabolism[108]. The psychotropic effect or "high" is observed to occur more quickly by the smoking than oral route and this is remarked by Iversen[109] as the reason "smoking is the preferred route of cannabis for many people". As with the administration by smoking the elimination phase from oral THC in plasma can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and beta half-life of 25 to 36h[110]. However, as noted above, the terminal half-life of THC can be much longer with considerable individual variability[111].

2.2.1.3 Rectal THC

In a pilot study[112] a suppository containing 11.8 mg of the THC hemisuccinate ester (equivalent to 9 mg THC) was administered to three women [two of whom had previously exhibited low plasma THC levels with a 10-mg dose of the oral THC (dronabinol, Marinol®)] provided comparatively high plasma THC concentrations. Areas under the curves for plasma THC were more than 30-fold higher than after oral dosing.. In another pilot study[113] in 2 patients with spasticity, multiple 10- 15 mg doses of oral THC (dronabinol, Marinol®) were compared with rectal THC hemisuccinate suppositories (2.5-5 mg) over 24 h. After oral doses, peak plasma levels from 2.1 to 16.9 ng/mL THC and 74.5 to 244.0 ng/mL metabolite were found. After rectal doses, peak plasma levels from 1.1 to 4.1 ng/mL THC and 6.1 to 42.0 ng/ml metabolite were measured over 8

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[105] A Ohlsson, JE Lindgren, A Wahlen, S Agurell, LE Hollister, HK Gillespie. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking..Clin Pharmacol Ther. 1980; 28: 409-416

[106] S Agurell, M Halldin, JE Lindgren , A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev. 1986; 38: 21-43.

[107] ME Wall, BM Sadler, D Brine, H Taylor, M Perez-Reyes. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther. 1983; 34: 352-363.

[108] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003, p 949.

[109] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 pp 46 -47.

[110] Marinol® U.S monograph Unimed Pharmaceuticals Inc. http://www.marinol.com/pdf/Marinol.pdf

[111] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[112] RD Mattes, LM Shaw, J Edling-Owens, K Engelman, MA Elsohly. Bypassing the first-pass effect for the therapeutic use of cannabinoids. Pharmacol Biochem Behav 1993; 44: 745-7.

[113] R Brenneisen, A Egli, MA Elsohly, V Henn, Y Spiess.The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther. 1996; 34: 446-52.

hours. Corrected for dose, rectal THC, was about twice as bioavailable as the oral dosage form. This is attributed to a lower absorption and higher first-pass metabolism from oral *vs*. rectal route.

2.2.2 Distribution

Distribution of THC begins immediately and rapidly after absorption. The plasma protein binding of THC and its metabolites is approximately 97%[114, 115]. THC is mainly bound to low-density lipoproteins, with up to 10% present in red blood cells[116], while the metabolite, 11-hydroxy THC, is even more strongly bound with only 1% found in the free-fraction[117].

THC has a large apparent volume of distribution, approximately 10 L/kg, because of its lipid solubility. Animal studies show that it is sequestered to the fat tissues including brain[118]. However, considerably less than 1 per cent of an administered dose reaches the brain[119, 120]. The highest concentrations are found in the heart and in adipose tissue, with levels reaching 10 and 1000 times that of plasma, respectively[121]. THC readily crosses the blood brain barrier and the slight delay in correlating peak plasma concentration to effects is assumed to reflect this distribution[122]. While immediate distribution is high in liver, spleen and body fat are the major sites of distribution after 72 h. Spleen and body fat are the long-term storage sites[123].

There has been concern about the possible consequences of the long persistence of THC in fatty tissues. However, there is no evidence that the THC residues persist in the brain. Release from the fatty storage sites into blood is so slow and low that levels attained are not high enough to cause psychological effects. However, with regular use THC will accumulate[124].

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[114] R Garrett, CA Hunt. Pharmacokinetics of delta-9-tetrahydrocannabinol in dogs. J Pharm Sci. 1977; 66:395-407.

[115] M Widman, S Agurell, M Ehrnebo, G Jones. Binding of (+)- and (minus)-delta-1-tetrahydrocannabinols and (minus)-7-hydroxy-delta-1-tetrahydrocannabinol to blood cells and plasma proteins in man. J Pharm Pharmacol. 1974; 26: 914-916.

[116] M Wahlqvist, IM Nilsson, F Sandberg, S Agurell. Binding of delta-1-tetrahydrocannabinol to human plasma proteins. Biochem Pharmacol. 1970 Sep;19(9):2579-84.

[117] M Widman, IM Nilsson, S Agurell, H Borg, B Granstrand. Plasma protein binding of 7-hydroxy- 1-tetrahydrocannabinol: an active 1-tetrahydrocannabinol metabolite. J Pharm Pharmacol. 1973 Jun;25(6):453-7.

[118] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999, pp 91-103.

[119] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[120] GG Nahas, HC Frick, JK Lattimer, C Latour, D Harvey. Pharmacokinetics of THC in brain and testis, male gametotoxicity and premature apoptosis of spermatozoa. Hum Psychopharmacol 2002; 17:103-113

[121] .EB Truitt Jr. Biological disposition of tetrahydrocannabinols. Pharmacol.Rev. 1971;23: 273-8.

[122] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

[123] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999, pp 91-103.

[124] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p 51.

2.2.3 Metabolism

Most metabolism of cannabinoids occurs in the liver and different metabolites predominate when different routes of administration are used. The complex metabolism of THC involves allylic oxidation, epoxidation, decarboxylation and conjugation[125]. Cannabinoids are good substrates for cytochrome P_{450} mixed-function oxidases and in humans the major site of hydroxylation is C-11, catalyzed by CYP 2C9[126]. This is considered for likely drug interactions. The major initial metabolites of THC are 11-hydroxy THC and 11-nor-9-carboxy THC. Over eighty other metabolites of THC, most of which are polar and acidic, have been identified and isolated by conducting *in vivo* experiments in humans or *in vitro* studies with human tissue[127]. 11-Hydroxy THC is rapidly formed by action of hepatic microsomal oxidases, and plasma levels parallel the duration of observable drug action. 11-hydroxy THC has been found to have psychotomimetic properties equal to THC[128, 129]. After smoking (1.75 and 3.55% THC cigarettes) this metabolite[130]appears rapidly and peaks shortly after THC, at about 15 minutes after the start of smoking. It exhibited peak plasma concentrations of about 7.5 ng/mL (about 5% of parent THC) and the AUC profile of this metabolite averaged 20% of the parent. Similar results were obtained with intravenous administration[131].

The psycho-inactive 11-nor-9-carboxy THC is the primary acid metabolite of THC excreted in urine[132] and it is the cannabinoid often screened for in forensic analysis of body fluids[133]. Peak plasma values of this metabolite occur 1.5 to 2.5 h after smoking and are about one third the concentration of parent THC. Following oxidation, the phase II metabolites of the free drug or hydroxy-THC appear to be glucuronide conjugates[134].

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[125] S Agurell, M Halldin, JELindgren , A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev. 1986; 38: 21-43.

[126] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999, pp 91-103.

[127] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[128] HD Christensen, RI Freudenthal, JT Gidley, R Rosenfeld, G Boegli, L Testino, DR Brine, CG Pitt, ME Wall. .Activity of delta-8- and delta-9-tetrahydrocannabinol and related compounds in the mouse. Science. 1971; 172: 165-167.

[129] M Perez-Reyes, MC Timmons, MA Lipton, KH Davis, ME Wall. Intravenous injection in man of 9 -tetrahydrocannabinol and 11-OH- 9 -tetrahydrocannabinol.. Science. 1972 ; 177: 633-635.

[130] MA Huestis, JE Henningfield, EJ Cone. Blood cannabinoids I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Analyt Tox, 1992; 16: 276-282.

[131] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[132] MA Huestis, JM Mitchell, EJ Cone. Urinary excretion profiles of 11-nor-9-carboxy-delta 9-tetrahydrocannabinol in humans after single smoked doses of marijuana. J Anal Toxicol. 1996; 20: 441-452.

[133] BR Martin, EJ Cone. Chemistry and pharmacology of cannabis. In The health effects of cannabis", eds H Kalant, W Corrigall, W. Hall. R Smart, Centre for Addiction and Mental Health, Toronto, 1999., pp21-68.

[134] S Agurell, M Halldin, JE Lindgren, A Ohlsson, M Widman, H Gillespie, L Hollister. Pharmacokinetics and metabolism of Δ^1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev, 1986; 38:21-43.

The metabolism of CBD and CBN in humans have not been fully described, but again the 11-hydroxy metabolite appears a major phase I product, but for CBD the amount of more polar metabolites appears greater than for THC[135]. For CBN, as well as the 11-hydroxy metabolites, dihydroxy -CBN, CBN-7-oic acid and more polar metabolites are reported [136].

It is known that polyaromatic hydrocarbons found in tobacco and cannabis smoke induce the action of CYP1A2. If it is shown that the metabolism of THC also involves this cytochrome P_{450}, then repeated exposure to cannabis could cause the more rapid disappearance of THC via this specific enzyme[137]. Various other cytochrome P_{450}, enzymes are of interest for potential drug interactions. In human liver microsome preparations, CBD has been shown to inhibit formation of THC metabolites catalyzed by CYP 3A, with less effect on CYP 2C9[138]. However, others suggest that CBD decreases formation of 11-hydroxy THC by inhibition of CYP 2C9[139]. Observed and potential interactions of cannabis with other drugs are discussed later.

After oral doses of THC, parent THC and its active metabolite, 11-OH-THC, are present in approximately equal concentrations in plasma[140,141]. Concentrations of both parent drug and metabolite peak at approximately 2 to 4 hours after oral dosing and decline over several days. Clearance averages about 0.2 L/kg-hr, but is highly variable, due to the complexity of cannabinoid distribution[142]. The larger amount of 11-hydroxy THC metabolite, from first pass metabolism by this route, which is similar in potency to THC, complicates interpretation of potential effects. With oral THC dosing, the absorption is slow and variable, and peak concentrations of THC may be considered one tenth those from efficiently smoked administration but the plasma levels of active 11-hydroxy metabolite are about 3 times higher than observed in the plasma from smoking [143] .

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[135] S Agurell, K Leander. Stability, transfer and absorption of cannabinoid constituents of cannabis (Hashish) during smoking. Acta Pharm Suecica, 1971;8: 391-402.

[136] M Perez-Reyes, MC Timmons, MA Lipton, KH Davis, ME Wall. Intravenous injection in man of 9 -tetrahydrocannabinol and 11-OH- 9 -tetrahydrocannabinol.. Science. 1972 ; 177: 633-635.

[137] E Valjent, JM Mitchell, MJ Besson, J Caboche, R Maldonado. Behavioural and biochemical evidence for interactions between Delta 9-tetrahydrocannabinol and nicotine. Br J Pharmacol. 2002; 135: 564-578.

[138] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999, pp 91-103.

[139] LM Bornheim, ET Everhart, J Li, MA Correia. Characterization of cannabidiol-mediated cytochrome P450 inactivation. Biochem Pharmacol. 1993; 45: 1323-1331.

[140] ME Wall, M Perez-Reyes. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol. 1981; 21(8-9 Suppl): 178S-189S.

[141] EJ Cone, RE Johnson, BD Paul, LD Mell, J Mitchell. Marijuana-laced brownies: behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J Anal Toxicol. 1988; 12: 169-75.

[142] Marinol® U.S monograph Unimed Pharmaceuticals Inc.

[143] ME,Wall, BM Sadler, D Brine, H Taylor, M Perez-Reyes. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther. 1983; 34: 352-63.

2.2.4 Excretion:
Elimination of THC and its metabolites occur via the faeces (65%) and the urine (20%). After five days, 80% to 90% of the total dose is excreted. Metabolites in the urine (of which there are 20) are mainly acidic such as 11-nor-9-carboxy THC. Those in the faeces are both acidic and neutral, the most abundant metabolites being 9-carboxy THC (29%) and 11-hydroxy THC (21%)[144, 145].

Similarly, following oral doses THC and its biotransformation products are excreted in both faeces and urine. Biliary excretion is the major route of elimination with about half of a radio labelled oral dose being recovered from the faeces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the faeces. Following administration of a single oral dose, low levels of THC metabolites have been detected for more than 5 weeks in the urine and faeces [146] [147]

It is important for patients to be aware that traces of marihuana can be detected in urine even for weeks[148] after dosing in forensic or employment situations when such testing may be applied.

2.3 Pharmacokinetic-pharmacodynamic relationships.

Most studies of plasma concentration – effect relationships for marihuana have been directed at the psychotropic effect ("the high") and the temporal relationship of plasma levels to this psychotropic effect and to intoxication and therefore impairment of cognitive or motor function is not clear[149]. The latter is of major forensic interest[150]. The acute effect on heart rate has also been used for such modelling[151]. Dose and plasma concentration *vs*. response for possible therapeutic applications are ill-defined, except for some information obtained for oral dosing with dronabinol (synthetic THC) for its limited indications[152]. Such correlations of THC pharmacokinetics are complicated by the

[144] RL Hawks. The constituents of cannabis and the disposition and metabolism of cannabinoids. NIDA Res. Monogr 1982;42:125-37.
[145] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999, pp 91-103.
[146] DJ Harvey. "Absorption, distribution and biotransformation of the cannabinoids". in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, 1999
[147] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.
[148] A Ohlsson, JE Lindgren, A Wahlen, S Agurell, LE Hollister, HK Gillespie. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking..Clin Pharmacol Ther. 1980; 28: 409-416
[149] S Harder, S Rietbrock. Concentration –effect relationship of delta-9-tetrahydrocannabinol and prediction of psychotropic effects after smoking marihuana. Int J Clin Pharmacol Ther. 1997; 35: 155-159.
[150] EJ Cone, MA Huestis. Relating blood concentrations of tetrahydrocannabinol and metabolites to pharmacologic effects and time of marijuana usage. Ther Drug Monit. 1993; 15: 527-532.
[151] G Barnett, CW Chiang, M Perez-Reyes, SM Owens. Kinetic study of smoking marijuana. J Pharmacokinet Biopharm. 1982; 10: 495-506.
[152] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003

emergence of active metabolites, particularly 11-hydroxy THC[153,154], which attains higher concentrations after oral than inhalation doses.

In experiments[155] with six volunteers who smoked 1 % by weight cigarettes with an average 894 mg (total THC dose 8.9 mg), a second cigarette was smoked after 2 hours. Plasma THC concentrations, heart rate and self-reported "high" profiles were documented. Similar psychological "high" occurred after both cigarettes, but less heart rate acceleration was found for the second cigarette. The heart rate for the first cigarette peaked at (average) 11 minutes after the start of smoking and was maintained until about 30 minutes after smoking. Thus, the effect was observed to begin at about 5 minutes after peak plasma concentration (mean 45 ng/mL)- exhibiting a lag time- and returned to baseline at approximately 30 minutes, when the plasma concentration was about 7 ng/ml. Although the heart rate increase was much smaller with the second cigarette, the lag time was similar. For the psychotropic effect, there was a different pattern with a gradual emergence of effect at 10 minutes (concentration 30 ng/mL, post peak) peaking at 30 minutes after smoking (concentration about 7 ng/mL) diminishing rapidly from 45 minutes after smoking (concentration 4.5 ng/mL). The second dose showed very similar pharmacokinetic and response profiles to the first cigarette. The data were fitted with a lag time model, since the effect emerges about 20 minutes after the peak plasma concentration. In another experiment this group examined the relationship between THC plasma concentrations and self-reported "high" with single cigarettes of three different potencies[156]. The cigarettes were 1.3, 2.0 and 2.5% in THC potency. As NIDA cigarettes average 900mg, the total dose available ranged from 11.7 to 22.5 mg. The results indicated a proportional dose response with the intensity and duration greatest for the 2.5%. As with the experiment above, there was a lag time from the plasma concentrations until the high and for the highest dose the feeling commenced at 5 minutes after smoking, when plasma concentration was about 140 ng/mL. However, with the lowest dose a similar intensity was noted at 5 minutes, at a concentration of 90 ng/mL (which appears near the peak concentration for this dose). For the low dose the intensity of the "high" reaches 50% of its maximum at 30 minutes and then gradually declines over 2 h, while for the high dose the "high" almost plateaus at 20 minutes for 60 to 75 minutes at 70% intensity, before declining. Modelling this data suggested that the steady state plasma concentration at 50% of the maximum high-effect, $C_{ss}(50)$, would be 25-29ng/mL[157].

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[153] ME Wall, M Perez-Reyes. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol. 1981; 21(8-9 Suppl): 178S-189S

[154] Cone, RE Johnson, BD Paul, LD Mell, J Mitchell. Marijuana-laced brownies: behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J Anal Toxicol. 1988; 12: 169-75.

[155]G Barnett, CW Chiang, M Perez-Reyes, SM Owens. Kinetic study of smoking marijuana. J Pharmacokinet Biopharm. 1982; 10: 495-506.

[156] CW Chiang, G Barnett. Marijuana effect and delta-9-tetrahydrocannabinol plasma level. Clin Pharmacol Ther. 1984; 36: 234-238.

[157]. CW Chiang, G Barnett. Marijuana effect and delta-9-tetrahydrocannabinol plasma level. Clin Pharmacol Ther. 1984; 36: 234-238.

Another report[158] shows a similar result with a 3.55% THC cigarette (which can yield an available dose of 32mg of THC). In this case the effect was perceptible within 2 to 3 minutes and exhibited a plateau, commencing at 9 minutes and continuing for 1.5 h, before diminishing over 3 to 4 h. A simultaneous average plasma concentration profile shows that at 1.5 h the THC level is about 10 ng/mL and the 11-hydroxy THC somewhat less. It is noted that the lack of correspondence of plasma profile and subjective "high" response can be fitted with a pharmacodynamic model with an "effect compartment" which, after a lag time, reaches equilibrium with an effect curve. After equilibrium is reached, intensity of effect is proportional to the plasma THC profile. This concentration–effect response demonstrates a counter-clockwise hysteresis.

This type of modelling[159] supports a 10 ng/mL cutoff[160] as evidence of functional impairment which is in agreement with the above $C_{ss}(50)$ estimate. The model was also used to simulate multiple dosing with a 1% cigarette containing 9 mg THC[161]. The duration of maximal "high" for this dose was estimated at about 45 minutes after dosing and declined to 50% of this peak effect at about 100 minutes following smoking. A dosing interval of 1h with this dose would give a "continuous high" and the recovery after the last dose would be 150 minutes. The peak plasma concentration during this dosage is estimated at about 70 ng/mL and the $C_{ss}(50)$ at about 30 ng/mL THC.

The data relating concentration to response is limited to the cardiac and subjective "high" responses and these show dissimilarities in profile. The information from oral dosing and with dronabinol is complicated by the larger amount of psychoactive 11-hydroxy THC metabolite that is formed by this route of administration. Thus, target THC plasma concentrations have only been derived based on the subjective "high" response that may or may not be related to the potential therapeutic applications. However, it is likely that the psychoactivity that elicits this response from the central nervous system is receptor derived and the concentrations are useful for suggesting doses from smoking.

3.0 Dosing

3.1 Smoking

The actual dose of THC absorbed when smoked is not easily quantified (see section 3.2.1). According to the World health organization[162], a typical joint contains between 0.5 and 1.0 g of cannabis plant matter (average 750 mg) which may vary in THC content

[158] EJ Cone, MA Huestis. Relating blood concentrations of tetrahydrocannabinol and metabolites to pharmacologic effects and time of marijuana usage. Ther Drug Monit. 1993; 15: 527-532.

[159] G Barnett, CW Chiang, M Perez-Reyes, SM Owens. Kinetic study of smoking marijuana. J Pharmacokinet Biopharm. 1982; 10: 495-506.

[160] AJ McBay. Cannabinoid testing: Forensic and analytical aspects. Lab management, 1985; 23: 36-41

[161] S Harder, S Rietbrock. Concentration –effect relationship of delta-9-tetrahydrocannabinol and prediction of psychotropic effects after smoking marihuana. Int J Clin Pharmacol Ther. 1997; 35: 155-159

[162] World Health Organization. Cannabis: a health perspective and research agenda, 1997 http://www.who.int/substance_abuse/docs/cannabis.pdf

between 7.5 and 225 mg (*i.e.* typically between 1 and 30 per cent; see table below). The actual amount of THC delivered in the smoke has been estimated at 20 to 70 per cent, the remainder being lost through combustion or sidestream smoke. The bioavailability of THC (the fraction of THC in the cigarette which reaches the bloodstream) from marihuana cigarettes in human subjects has been reported from 5 per cent to 24 per cent. The amount of other cannabinoids, mainly CBN and CBD, is usually much less, but the amount delivered and absorbed parallels that of THC.

Recent seized samples (Health Canada, personal communication) found a mean of about 10% THC (range 3-30%). If a joint contains 750 mg of cannabis plant matter, then it might contain an average of 75mg (range 30-300mg) THC. Table 4 shows some relationships between % THC in cannabis plant material and amount in average joints

Table 4 Relationship of THC percent in plant material to available dose in a joint

%THC	mg per100mg cannabis	mg per 750 mg* " average joint"
1	1	7.5
2.5	2.5	18.75
5	5	37.5
10	10	75
15	15	112.5
20	20	150
30	30	225

*** WHO average weight**

However, the actual amount of cannabinoid taken up (bioavailability) depends greatly on smoking technique (likely maximum approximately 50% availability).

If a desired peak plasma concentration from smoking THC is in the 50-100 ng/mL range (see Section 2.3) it has been shown[163] that this can be readily achieved with smoke from a single 3.55 % marihuana cigarette with about 900 mg plant material (approximately 32 mg THC).

Another comparison of exposure per cigarette, is with the oral dose of THC (Marinol®) for the approved indication (see section 4.0) which is 2.5 mg to a maximum 20 mg/day, administered in equally divided doses every four to six hours (four times daily)[164]. Oral bioavailability is poor with only 10 to 20% of the dose reaching the systemic circulation. At the highest dose of 20 mg/day, 5 mg single doses would likely yield peak concentrations of 2.5 to 5ng/mL THC (or perhaps, including the 11-hydroxy-metabolite, an equivalent of 5 to 10 ng/mL active drug) and the time to peak is 2 to 4 h. In contrast it has been shown that a 3.55% THC cigarette, with an available 32 mg total dose yields an

[163] MA Huestis, AH Sampson, BJ Holicky, JE Henningfield, EJ Cone. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther. 1992 ; 52: 31-41,

[164] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

average peak plasma concentration of 152 ± 86 ng/mL and the time to peak is 6 to 9 minutes[165]. On this basis a 750 mg joint of 5% strength with 37.5 mg total THC (see table 3) would yield slightly higher plasma levels and if the current average "street" marihuana is 10% THC , then plants yielding joints from such a source might have an available 75mg dose and could result in rapid attainment of plasma concentrations above 300 ng/mL. Clearly even more potent strains of cannabis have been reported (see section 1.2). ***Thus patients initiating smoked marihuana therapy should be cautioned to begin slowly and to stop smoking if tachycardia occurs***.

3.2 Oral

There is little information on marihuana administered orally, except for the dronabinol (Marinol®)[166] administered in oil contained in a capsule. A common method of making cookies is described in section 1.2.2 and this process would liberate THC from any tetrahydro-cannabinolic acid present. This release of acid is less certain if plant material is infused with hot or boiling water. The pharmacokinetic information described in section 2.2 reports the erratic and slow absorption from the oral route and doses are estimated from the information for Marinol®. From that it appears that 2.5 to 5 mg of THC should be contained in each dose, which from Table 3, would suggest that 50 mg of 5% THC plant material or 25 mg of 10% plant material would be required in cookies for the lower dose.

4.0 Purported Indications and Clinical Use

The oral form of synthetic THC, dronabinol (2.5, 5 or 10 mg, dissolved in sesame oil) in capsules is marketed in the US and Canada as Marinol® . It is indicated for treatment of chemotherapy-induced emesis and for appetite stimulation in AIDS- related anorexia associated with weight loss[167, 168]

While there are many anecdotal reports of the therapeutic value of smoked marihuana, scientific studies supporting the safety and efficacy of marihuana for therapeutic claims are inconclusive. The existing scientific evidence for various symptoms is summarized in the following sections.

4.1 Nausea and vomiting

Although progress in controlling emesis associated with chemotherapy has been made with improved regimens of older anti-emetics like prochlorperazine and with introduction of newer agents, including the 5 HT_3 receptor-antagonists (*e.g.*, ondansetron,

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[165] MA Huestis, AH Sampson, BJ Holicky, JE Henningfield, EJ Cone. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther. 1992 ; 52: 31-41,

[166] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[167] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[168] Marinol® U.S monograph Unimed Pharmaceuticals Inc. http://www.marinol.com/pdf/Marinol.pdf

granisetron), nausea and vomiting remain major concerns for patients[169]. Of all the potential medicinal uses of cannabinoids, most information is available on nausea and vomiting caused by cancer drugs[170] . There are also many patient claims that smoked cannabis relieves nausea and vomiting associated with cancer chemotherapy. However, many trials were uncontrolled and most of the trials studied oral cannabinoids, including the synthetic nabilone and THC. In some of the trials, the oral cannabinoid was of equal effectiveness to the older anti-emetics, but in some trials they were found less effective. There were no trials of oral cannabinoids against the newer 5-HT_3 receptor antagonists (such as ondansetron). Moreover the side-effects of these oral cannabinoids, including drowsiness, dry mouth, visual disturbances and ataxia, appeared greater than those with standard drugs[171]. A recent meta-analysis[172] quantitating safety and efficacy compared 30 clinical trials for control of chemotherapy-induced nausea, but no trials for smoked cannabis were found acceptable for comparison. The trials of the oral cannabinoids, including 16 for nabilone and 13 for synthetic THC (dronabinol), found them to be slightly superior to conventional (older) antiemetics, such as prochlorperazine and metoclopramide, and patients preferred them. However, the major limitations, even for short term use, are potentially serious side effects such as dysphoria, depression, paranoia and hallucinations. For some patients, the mood enhancing effects may suggest their use as adjuvants for control of emesis caused by chemotherapy.

In one trial, fifteen patients with osteogenic sarcoma receiving high-dose methotrexate chemotherapy, oral and smoked THC were studied as anti-emetics in a randomized, double-blind, placebo-controlled trial[173]. The dosage of oral THC was 10mg/m^2 every 3 hours and, if vomiting occurred, 17 mg by smoking. Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo. THC was significantly more effective than placebo in reducing the number of vomiting and retching episodes, degree of nausea, duration of nausea, and volume of emesis ($P < 0.001$). There was a 72% incidence of nausea and vomiting on placebo. When plasma THC concentrations measured less than 5.0 ng/mL, 5.0 to10.0 ng/mL, and greater than 10.0 ng/mL, the incidences of nausea and vomiting were 44%, 21%, and 6%, respectively. THC was concluded to have significant antiemetic properties and the smoked product provided higher THC concentrations.

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[169] RJ Gralla. "Cannabinoids and the control of chemotherapy-induced nausea and vomiting " in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, 1999. pp 599-610.

[170] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997.p 23.

[171] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997.p 23

[172] MR Tramer, D Carroll, FA Campbell, DJ Reynolds, RA Moore, HJ McQuay. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001; 323: 16-21.

[173] AE Chang, DJ Shiling, RC Stillman, NH Goldberg, CA Seipp, I Barofsky, RM Simon, SA Rosenberg. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Ann Intern Med. 1979; 91: 819-824.

In a single-arm, open-label study, seventy four patients receiving a variety of chemotherapeutic agents, in whom standard antiemetic agents had failed, were administered cannabis in the form of 'joints'. Sixteen withdrew from the trial because they found the smoke too harsh. The remaining 56 patients were asked to rate the effectiveness of marihuana compared to previous chemotherapy cycles. Forty-four (78%) subjects rated the treatment as moderately or highly effective (34% latter) in symptom relief. The most common side effects were sedation (88%), dry mouth (77%) and dizziness (39%) with 13% of patients experiencing no side effects at all[174]. A Canadian study[175] compared oral THC with inhaled marihuana in a double-blind cross-over experiment with placebo cigarettes. The chemotherapy included anthracyclines (cisplatin, 60%, doxorubicin, 85% or cyclophosphamide, 75%) and results indicated similar emesis control for the two THC treatments with 25% reporting full control. Patients expressed a similar preference for both treatments, with a slightly higher acceptance for oral drug. Plasma level measurements did not show higher levels of THC or metabolite for the smoked marihuana.

It is suggested that the age of patients exposed to inhaled cannabis for control of emesis is a factor in acceptance. Two trials in which patients continued to have emesis when treated with oral THC were reviewed[176]. In one trial of younger subjects marihuana was smoked every 3 to 4 hours for several days and yielded "higher" levels of THC in plasma than oral drug with significant anti-emetic effect. The median age in the study was 24 years. In another study negative results were obtained in an older subject group (median age 41). It is averred that lack of experience in smoking the drug resulted in ineffective plasma levels being attained[177].

A meta analysis of antiemesis studies of oral and smoked marihuana in seven US states was prepared[178], mainly in cancer chemotherapy patients. The conclusions from these uncontrolled trials were that smoked marihuana is (at least) 70% effective in blocking emesis caused by chemotherapy and patients prefer smoking marihuana over oral THC (capsule) or traditional anti-emetics. This is attributed to achievement of more reliable blood levels by smoking and perhaps because cannabinoids other than THC modulate the outcome. The side effects of smoked marihuana were sedation (mainly) and some dizziness with some "smoke aversion". The oral THC side effects documented included "extreme" sedation, dysphoria and disorientation of various types and "inability to keep the pill down".

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[174] V Vinciguerra, T Moore, E Brennan. Inhalation marijuana as an antiemetic for cancer chemotherapy. N Y State J Med. 1988; 88: 525-527

[175] M Levitt, C Faiman, R Hawks. Randomized double-blind comparison of delta-9 tetrahydrocannabinol (THC) and marihuana as chemotherapy anti-emetics. Proc Am Soc Clin Oncol, 1984; 3: 91

[176] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000, p 144.

[177] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p. 144

[178] R Musty. Meta-analysis of state clinical cancer studies on the efficacy of cannabis. Presentation to the First National Clinical Conference on Cannabis Therapeutics. Medical marihuana: Science-based Applications, Iowa City Iowa, April 6-8, 2000.

The IOM[179] and other committees[180]consider that the place (if any) for smoked marihuana would be as an adjunct to other anti-emetics, when they are not fully successful in treatment. However, there are no trials available for guidance. The BMA report[181] indicates the research needed to evaluate marihuana in chemotherapy-induced emesis. This includes establishing dose ranges for cannabinoids and clinical trials to differentiate optimum cannabinoid treatment for specific anti-cancer agents and patient groups.

The IOM report[179] suggests that, since there are now more effective antiemetic agents available than were available in the 1980s (especially the 5 HT_3 receptor antagonists), patients are less in need of THC. Although cannabinoids are only modest antiemetics, however, in particular patients who respond poorly to currently used antiemetic drugs, they might be effective in some cases, or might be more effective in combination with a new drug.

The relationship of the marihuana "high" or euphoria to duration of anti-emesis has not been properly evaluated. While some people who spoke to the IOM study team described the mood-enhancing and anxiety-reducing effects of marihuana as a positive contribution to the antiemetic effects of marihuana, 25% of the patients in one study were unable to tolerate smoked marihuana because of smoke irritation[179]. Some investigators suggest that older patients may be less tolerant to the marihuana "high" than younger patients, since the latter group possibly had experienced the drug recreationally. Overall, the effects of oral THC and smoked marihuana are similar, but there are differences. For example, in investigations with experienced marihuana users, subjects reported that marihuana made them feel "mellow," whereas comparable doses of oral THC did not. Such differences might be due to the different routes of delivery of THC, as well as the different mixture of cannabinoids found in the marihuana plant. These influences have not been researched.

4.2 Wasting syndrome (cachexia, *e.g.*, from tissue injury by infection or tumor) and loss of appetite (anorexia) in AIDS and cancer patients:

The IOM report following review of treatment of AIDS wasting syndrome and terminal cancer concludes that cannabinoid drug effects are promising for treating wasting syndrome in AIDS patients[182]. Nausea, appetite loss, pain, and anxiety are all afflictions of wasting, and all can be mitigated by marihuana.

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[179] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999, p 4.17.
[180] Working Party on the Use of Cannabis for Medical Purposes, Health Department of New South Wales, Australia, 2000, Vol II, p 41. http://www.druginfo.nsw.gov.au/druginfo/reports/canrep2.pdf .
[181] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p27.
[182] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999, p4.22.

4.2.1 To stimulate appetite and produce weight gain in AIDS patients.
Current treatment approaches to HIV-wasting include nutritional supplements, appetite-stimulating drugs, testosterone, testosterone analogues, and other anabolic steroids and growth hormone[183].

The reports that marihuana is beneficial for patients with AIDS wasting syndrome are anecdotal, although it appears to be very popular with AIDS patients[184]. There have been laboratory studies with healthy subjects that confirm an appetite stimulating effect of smoked marihuana together with increases of food consumption and body weight[185,186] . In a controlled, residential laboratory sudy in which food consumption was carefully monitored and cannabis cigarettes were smoked with a standardized procedure, subjects consumed significantly more calories daily compared to placebo [187]. There are, however no clinical trials of the smoked drug for this indication[188].

Oral synthetic THC, dronabinol, administered as capsules (Marinol®) has been approved for this indication and there are several clinical trials[189]. The Marinol product monograph summarizes a randomized double-blind, placebo controlled-trial in 139 patients[190] with the 72 patients in the treatment group initially receiving 2.5 mg dronabinol twice a day, but then having the dose reduced to 2.5 mg at bedtime due to side effects (feeling high, dizziness, confusion and somnolence). Over the six week treatment period dronabinol significantly increased appetite, with a trend towards improved body-weight, and mood, and a decrease in nausea. After the six weeks, patients were allowed to continue receiving dronabinol, during which the appetite improvement continued.

A randomized, open-label study compared dronabinol 2.5 mg twice per day and megestrol acetate (250 or 750 mg/day) alone and in combination over 12 weeks in

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[183] American Medical Association, Council of Scientific Affairs 1997. Medical Marijuana, Chicago, IL http://www.ama-assn.org/ama/pub/article/2036-6124.html#major_proposed_medical_uses
[184] L Grinspoon, JB Bakalar Marijuana the forbidden medicine, Yale University Press, Newhaven, 1993.
[185] RD Mattes, K Engelman, LM Shaw, MA Elsohly. Cannabinoids and appetite stimulation. Pharmacol Biochem Behav. 1994; 49: 187-195.
[186] RW Foltin, MW Fischman, MF Byrne. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite. 1988; 11: 1-14.
[187] RW Foltin, MW Fischman, MF Byrne. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite. 1988; 11: 1-14.
[188] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p4.19
[189] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.
[190] JA Beal, R Olson, L Laubenstein, JO Morales, P Bellman, B Yangco, L Lefkowitz, TF Plasse, KV Shepard. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Management, 1995; 10: 89-97.

52 patients suffering HIV wasting syndrome[191]. Dronabinol alone, or in combination with 250 mg megestrol, was not associated with weight gain, which was significant with the high dose megestrol. Side effects on the THC treatment arms included CNS events such as euphoria, confusion and hallucinations. The pharmacokinetic values (plasma profile over 24 h after dose at 2 weeks of treatment) showed large inter-patient variations,*e.g.*, the peak concentrations for THC ranged from 0.58 to 12.48 ng/mL and the 11-hydroxy THC level, which was about 2 to 4 times that of parent THC, ranged from 0.52 to 37.5 ng/mL.

A major concern with marihuana smoking in HIV-infected patients is that they might be more vulnerable than other marihuana users to immunosuppressive effects of marihuana or to the exposure of infectious organisms associated with marihuana plant material[192]. There are also drug interaction concerns that are reviewed later.

4.2.2 To stimulate appetite and produce weight gain in cancer patients.
Smoked marihuana has not been studied in patients with cancer cachexia. Oral THC (dronabinol) is the only cannabinoid examined for treating cachexia in cancer patients and this has been shown to improve appetite and food intake from observations during the investigations of the anti-nausea effect[193,194]. Improved appetite and increased food intake was reported in patients with unresectable or advanced cancer treated with open-label dronabinol 2.5 mg 2 to 3 times daily for 4 to 6 weeks, but weight gain was achieved in only a few patients[195,196,197]. Modest weight gain was obtained with a larger dose regimen of dronabinol (5 mg, 3 times daily), but the CNS side effects including dizziness and somnolence were limiting[198]. Cancer cachexia is not an approved indication for dronabinol either in Canada or the U.S.

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[191] JG Timpone, DJ Wright, N LI, MJ Egorin, ME Enama, J Mayers, G Galetto and the DATRI 004 study group. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. in Marihuana and Medicine. Eds GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, 1999. pp 701-716.

[192] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p4.19

[193] H Ekert, KD Waters, IH Jurk, J Mobilla, F Loughnan. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Aust. 1979;2:657-659.

[194] SE Sallan, C Cronin, M Zelen, NE Zinberg. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med. 1980;302:135-138.

[195] TF Plasse, RW Gorter, SH Krasnow, M Lane, KV Shepard, RG Wadleigh. Recent clinical experience with dronabinol. Pharmacol Biochem Behav. 1991;40: 695-700

[196] R Wadleigh, GM Spaulding, B Lumbersky, *et al*. Dronabinol enhancement of appetite in cancer patients. Proc Am Soc Oncol. 1990; 9: 331.

[197] K Nelson, D Walsh, P Deeter, F Sheehan. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. J Palliative Care. 1994; 10: 14-18.

[198] W Regelson, JR Butler J,, Schulz et al. Delta-9-tetrahydrocannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: Braude MC, Szara S, eds. The Pharmacology of Marihuana: A Monograph of the National Institute on Drug Abuse. New York: Raven Press; 1976;763-776.

The immunomodulating effects of some cannabinoids could be contraindicated in some cancer patients (both the chemotherapy and the cancer can be immunosuppressive)[199].

4.2.3 Anorexia nervosa

Anorexia nervosa is another disease involving life-threatening weight loss. Only one published report concerned a randomized trial of oral THC[200] which was unsuccessful for weight gain and with three of the eleven patients administered THC reporting severe dysphoric reactions. Both the British Medical Association[201] and IOM[202] conclude that marihuana is unlikely to be effective in this group of patients. However, smoked marihuana has not been studied and further work may be necessary to draw conclusions about treatment of anorexia nervosa.

4.3 Multiple sclerosis, spinal cord injury or disease

The common symptom of these diseases is muscle spasticity.

There are many anecdotal reports that marihuana can ameliorate spasticity associated with multiple sclerosis or spinal cord injury when other drugs failed or produce unacceptable side-effects[203, 204,205]. Also experiments with animals have shown that cannabinoids affect motor areas in the brain that might influence spasticity[206].

4.3.1 Multiple sclerosis (MS)

Published reports spanning one hundred years suggest that people with spasticity may experience relief with cannabis[207]. As many as 4% of MS patients in the UK already smoke cannabis to relieve symptoms [208] and in a mail survey of 233 MS

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[199] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 4.21

[200] H Gross, MH Egbert, VB Faden, SC Godberg, WH Kaye, ED Caine, R Hawks, NE Zinberg. A double-blind trial of delta-9-THC in primary anorexia nervosa. J Clin Psychopharmacology, 1983; 3: 165-171.

[201] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997.p 46

[202] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p4.21.

[203] American Medical Association, Council of Scientific Affairs 1997. Medical Marijuana, Chicago, IL http://www.ama-assn.org/ama/pub/article/2036-6124.html#major_proposed_medical_uses p 10.

[204] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 30.

[205] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 4.23.

[206] P Consroe. Clinical and experimental reports of marihuana and cannabinoids in spastic disorders. In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999, chapter 52, pp 611-617.

[207] P Consroe, SR Snider: Therapeutic potential of cannabinoids in neurological disorders, in: R Mechoulam (ed.) Marijuana/Cannabinoids as therapeutic agents. 1986, CRC Press, Boca Raton, FL, 21-49.

[208] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p 157

patients in the UK and US , 112 (48%) reported[209] that cannabis was used to ameliorate symptoms.

There have been three clinical trials that examined the effect of oral cannabinoids (dronabinol, Marinol®) in MS involving a total of 30 patients. In an open trial of 5 to 15 mg oral THC every 6 hours involving 8 MS patients[210], 5 patients reported subjective improvement in motor co-ordination and in 2 patients tremor was objectively improved. A double-blind placebo-controlled study of 5 and 10 mg oral THC in single doses among 9 patients found improvement in spasticity based on examiner ratings[211]. A double-blind, placebo-controlled crossover, dose-escalation trial of 2.5 to 15 mg oral THC once or twice daily for five days among 13 MS patients found subjective improvement in spasticity at doses of 7.5 mg or higher, but no changes in objective measures of spasticity or weakness were observed[212]. In a placebo-controlled study of the synthetic cannabinoid, nabilone, in one MS patient, the patient reported increased well-being, less frequent nocturia and reduced severity of muscle spasticity during the nabilone phase[213]. In the one double-blind placebo controlled, trial [214]of smoked cannabis (1.54% THC single cigarette dose) postural control was measured in10 patients with MS and 10 controls. Posture and balance was impaired in all subjects, but this effect was greater in the MS patients. Some patients claimed subjective improvement as well as experiencing the marihuana "high".

4.3.2 Spinal cord injury

Those patients surviving spinal cord injuries are usually young (60% less than 35 years old[215]), and require long-term or even life-long care. While there are no clinical trials of smoked marihuana for treatment of muscle spasms, spinal patients reported to the IOM workshops that muscle spasms, nausea and sleeplessness were alleviated by smoking marihuana. In one survey, 10 patients with various problems related to spinal cord injury responded concerning effects of cannabis[216]. Improvement in spasticity and headache were noted by five patients and four of nine patients reported phantom limb pain amelioration, but two of the ten reported worsening of urinary retention. A questionnaire with responses from 24 of 48 spinal patients who used

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[209]Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur Neurol 1997;38(1):44-8

[210] DB Clifford. Tetrahydrocannabinol for tremor in multiple sclerosis. Ann Neurol. 1983;13 :669-671.

[211] DJ Petro, C Ellenberger Jr. Treatment of human spasticity with delta 9-tetrahydrocannabinol. J Clin Pharmacol. 1981; 21(8-9 Suppl): 413S-416S.

[212] JT Ungerleider, TA Andrysiak, L Fairbanks, GW Ellison, LW Myers. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv. Alcohol Subst Abuse, 1987; 7: 39-50.

[213] CN Martyn, LS Illis, J Thom. Nabilone in the treatment of multiple scelerosis. Lancet, 195, 345: 579

[214] HS Greenberg, SA Werness, JE Pugh, ROAndrus, DJ Anderson, EF Domino. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. Clin Pharmacol Ther. 1994; 5: 324-328.

[215] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 4.28

[216] M Dunn, R Davis. The perceived effects of marijuana on spinal cord injured males. Paraplegia, 1974; 12: 175

cannabis reported that 22 found decrease in spasticity from its use[217] . In a larger survey of 106 spinal patients by mail[218] 90% reported that marihuana helped control symptoms of muscle spasms in limbs and also improved urinary function.

There are few clinical reports of use of cannabinoids with this patient group. There is a case report of relief of spasms in a single patient with spinal cord injury[219]. Another single patient double-blind, randomized, balanced-order study compared oral 5 mg THC, oral codeine (50 mg) and placebo[220]. Each treatment was administered 18 times over 5 months during which the patient was also treated with baclofen and clonazepam. The THC provided antispasmodic and analgesic effects, while codeine only alleviated pain. An abstract[221] reported a double-blind, placebo controlled, randomized study of oral THC (35 mg) in which 2 of 5 paraplegic patients described improvements in reflex activity and stretch resistance. A pilot study[222] in 2 patients with organically caused spasticity, compared multiple doses of oral THC (dronabinol, Marinol®) 10- 15 mg and rectal THC hemisuccinate suppositories (2.5-5 mg) over 24h. Objective improvements in spasticity, rigidity and pain were reported, but there were no differences in mood, concentration ability or cardiovascular function seen after administration of THC. The THC bioavailability from rectal administration appears to be twice that from oral dosing.

4.4 Epilepsy

While some work in animals suggests that cannabinoids could have a role in treatment of some types of epileptic seizures[223], (in particular CBD appeared to have anticonvulsant without psychoactive properties[224]), there are only anecdotal and individual case reports that marihuana controls seizures in epileptics. In one single case report[225] and two anecdotal reports, patients with general, partial or absence seizures appeared to improve with smoking cannabis, in one case allowing reduction of dose of standard medication.[226].

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[217] J Malec, RF Harvey, JJ Cayner. Cannabis effect on spasticity in spinal cord injury. Arch Phys Med Rehabil. 1982; 63: 116-118.

[218] P Consroe, 1998, reported in LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000, p 163.

[219] DJ Petro. Marihuana as a therapeutic agent for muscle spasm or spasticity. Psychosomatics. 1980; 21: 81-85.

[220]M Maurer, V Henn, A Dittrich, A Hofmann. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci. 1990; 240: 1-4.

[221] WC Hanigan, R Destree, XT Troung. The effect of delta-9-tetrahydrocannabinol for the treatment of human spasticity. Clin Pharmacol therap, 1986; 198: Abstract B45.

[222] R Brenneisen, A Egli, MA Elsohly, V Henn, Y Spiess.The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther. 1996; 34: 446-52..

[223] P Consroe, R Sandyk. Potential role of cannbinoids for therapy of neurological disorders. In Marijuana/Cannabinoids: Neurobiology and Neurophysiology, eds. A Bartke and L Murphy, CRC Press, Boca Raton, FL, 1992 pp 459-524.

[224] LE Hollister .Health aspects of cannabis. Pharmacol Rev. 1986; 38: 1-20.

[225] PF Consroe, GC Wood, H Buchsbaum. Anticonvulsant nature of marihuana smoking. JAMA. 1975; 234: 306-307.

[226] L Grinspoon, JB Bakalar Marijuana the forbidden medicine, Yale University Press, Newhaven, 1993.

However, in another case smoking may have induced convulsions [227]. There is one epidemiological study[228] of 308 patients admitted to hospital after the first seizure, compared to 294 controls, reporting that there is weak evidence that marihuana use may be a protective factor against seizures in men but not in women.

The potential antiepileptic activity of cannabidiol (CBD) in epileptic patients who were poorly controlled with conventional anticonvulsants, has been investigated but is not promising. Two studies[229, 230] (available only in abstract) with a total of 22 epileptic patients reported no significant effect on seizure frequency with oral CBD (200-300 mg/day) *vs*. placebo. Another double-blind, placebo controlled trial, in 15 epileptic patients, who were not adequately controlled on conventional anti-convulsants, found that addition of oral CBD, 200-300 mg/day to the patients, regular medications for 4.5 months, improved control in 7 of the 8 patients on CBD with somnolence a side-effect in 4 patients[231].

4.5 Pain

While there are a variety of analgesic agents available for pain control, there are many patients who still suffer from intractable pain. A telephone survey about use of marihuana in the general Canadian population[232] had a 67.4% response rate and a weighted sample of 1.9% reported use for a medical reason in the year before the survey; 85% of those for pain and nausea.

There are no controlled clinical trials of smoked marihuana in treatment of pain. One report[233] of three patients with severe pain (one with a brain tumour), uncontrolled with opiates, and one patient with migraine found relief in all cases, with no "high". Another case reports relief from rheumatoid arthritis pain, as well as spasms and depression[234]. This is somewhat similar to the relief of painful muscle spasms from smoked cannabis, reported by one MS and one spinal cord patient [235]. A Canadian survey[236] of 15 patients

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[227] MH Keeler, CB Reifler. Grand mal convulsions subsequent to marijuana use. Case report. Dis Nerv Syst. 1967 ; 28 (7 Pt 1):474-475.

[228] SKC NG, JCM Brust, WA Hauser, M Susser. Illicit drug use and the risk of new-onset seizures. Amer J Epidem, 1990; 132: 47-57.

[229] FR Ames, S Cridland. Anticonvulsant effect of cannabidiol. S Afr Med J. 1986; 69:14.

[230] B Trembly, M Sherman. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Presented at Conference on cannabis and cannabinoids, Kolympari,1990, cited in British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997.p51.

[231] JM Cunha, EA Carlini, AE Pereira, OL Ramos, C Pimentel, R Gagliardi, WL Sanvito, N Lander, R Mechoulam. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980; 2: 175-85.

[232] AC Ogborne,RG Smart, EM. Adlaf Self-reported medical use of marijuana: a survey of the general population.Can Med Assoc J 2000;162: 1685-1686.

[233] L Grinspoon, JB Bakalar Marijuana the forbidden medicine, Yale University Press, Newhaven, 1993.

[234] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p 155.

[235] Petro DJ.Marihuana as a therapeutic agent for muscle spasm or spasticity. Psychosomatics. 1980;21: 81- 85.

[236] M Ware, A Gamsa, J Persson, M-A Fitzcharles. Cannabis for chronic pain: case series and implications. Pain Res Manage, 2002; 7: 95-99.

(10 men) who self-treated with cannabis for chronic pain from a variety of syndromes from chronic pancreatitis to MS, involved about half for musculoskeletal pain, including two patients with rheumatoid arthritis and four with severe back pain. All patients smoked herbal cannabis: 10 in joints, three in pipes and two in both forms. In addition two patients ate the cannabis and one took it in tea. The dosing was categorized into two groups: night time (7) and daytime (8), with the median single night time dose eight puffs (range 2 to 8) and that for day users three puffs (range 2 to 8 puffs) and a frequency from one to 16 times per day, but the most common dose was one joint per day, either as one dose or divided. However, twelve patients documented amelioration of pain with improved mood and 11 improved sleep. From such a survey there is little information on dose strength, but the experience of the "high" was associated with individual dose size.

4.5.1 Cancer pain

There are two double-blind, controlled studies of oral THC (dronabinol) in cancer pain. The first[237] was a dose ranging study of 5, 10, 15 and 20 mg THC, given in successive days, to ten cancer patients. Significant pain relief was found at the 15 and 20 mg dose levels, but at these higher doses patients were heavily sedated with mental clouding common. A second, placebo-controlled, study[238] compared oral 10 and 20 mg THC with 60 and 120 mg codeine in 36 patients with cancer pain. The 10 and 20 mg THC were equivalent in analgesic potency with 60 and 120 mg codeine respectively. The 10 mg THC dose was well tolerated and, despite its sedative effect, may have analgesic potential., but the 20 mg THC induced side effects that would prevent its therapeutic use, including somnolence, dizziness, ataxia, and blurred vision. Alarming extreme anxiety was also observed at this dose and 5 of 36 patients were eliminated from the study. The above result of the side effect profile is supported by a report concerning a synthetic analogue of THC also tested in controlled trials[239] and while it was equivalent in efficacy to codeine, it was not considered clinically useful because of the frequency of side effects.

4.5.2 Other pain categories

Intravenous THC (0.22mg/Kg and 0.44 mg/Kg) has been administered to patients undergoing tooth extraction[240]and compared to diazepam (0.157 mg/kg). High dose THC was least effective and diazepam most effective and four patients preferred placebo to low dose THC. A study of oral CBD, 450 mg/day in divided doses, in 10

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[237] R Noyes Jr, SF Brunk, DA Baram, A Canter. Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol. 1975; 15: 139-143.

[238] R Noyes Jr, SF Brunk, DA Avery, AC Canter. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther. 1975; 18: 84-89.

[239] M Staquet, C Gantt, D Machin. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. Clin Pharmacol Ther. 1978; 23: 397-401.

[240] D Raft, J Gregg, J Ghia, L Harris. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. Clin Pharmacol Ther. 1977; 21: 26-33.

patients with chronic neuropathic pain (neuralgia, etc.) also found no significant pain relief[241].

From receptor studies it appears that cannabinoids might be useful adjuncts to opioid analgesia[242]. Also, several reports of improvement of phantom limb pain have been documented from patients taking cannabis[243].

From some of the reports [244], [245] it appears that marihuana may ameliorate more than one symptom of some of the diseases treated. For example, with spasticity, there is usually pain and THC might be effective.

A meta-analysis of all cannabinoid trials for analgesia has been completed[246]. No trial tested cannabis, but several cannabinoids were studied in 20 identified randomized controlled trials, 11 of which were excluded. Of the 9 trials included (222 patients), 5 trials related to cancer pain, 2 to chronic non-malignant pain, and 2 to acute postoperative pain. The conclusion was that, as well as having effects on the CNS that limit their use, cannabinoids are no more effective than codeine as analgesics.

4.6 Other diseases and symptoms

There are other diseases and symptoms for which marihuana has been claimed to have some potential benefits. These diseases and symptoms include movement disorders, glaucoma, bronchial asthma, hypertension, mood disorders and psychiatric conditions.

4.6.1 Movement disorders

The movement disorders most often considered for marihuana or cannabinoid therapy are dystonia, Huntington's disease, Parkinson's disease, and Tourette's syndrome. A recent paper considers the role of the endogenous cannabinoid system which appears to be intricately involved in normal physiology, specifically in the control of movement, formation of memories and appetite control. The system may be involved in the pathology of several neurological diseases and recent progress in understanding the contribution of endocannabinoids to the pathology and towards the design of therapy of Huntington's disease, Parkinson's disease and tremor has been

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[241] P Lindstrom, U.Lindblom, LBoreus. Lack of effect of cannabidiol in sustained neuropathia. , presented at Marihuana International Conference, Melbourne, 1987, cited from British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 43.

[242] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 4.8.

[243] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 43.

[244] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000, p 157

[245] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p44.

[246] FA Campbell, MR Tramer, D Carroll, DJ Reynolds, RA Moore, HJ McQuay. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ. 2001; 323: 13-16.

reviewed[247].

Movement disorders are often transiently exacerbated by stress and activity and improved by factors that reduce stress. This is of particular interest because for many people marihuana reduces anxiety.

4.6.1.1 Dystonia

No controlled study of smoked marihuana in dystonic patients has been published. However, there was a preliminary open trial[248] of an oral cannabinoid. CBD, administered in five dystonic patients with100mg/day rising to 600 mg/day over 6 weeks, was reported to show modest dose-related improvements in all five, but there was worsening of tremor and hypokinesia in 2 patients with co-existing Parkinson's disease. Results of a double-blind randomized, placebo-controlled study of a synthetic cannabinoid (nabilone) showed no significant reduction in dystonia[249].

4.6.1.2 Huntington's disease

A double-blind, placebo-controlled trial[250] of oral CBD, 10mg/kg/day in 15 patients with Huntington's disease found no beneficial effects of treatment .

4.6.1.3 Parkinson's disease.

There are theoretical reasons from research on brain transmission pathways that support a role for cannabinoids in the treatment of Parkinsonism. However, the one published clinical trial of smoked marihuana (1 gram cigarettes containing 2.9% THC) involving five cases of idiopathic Parkinson's disease[251] found no improvement in tremor after the patients smoked marihuana, whereas all subjects benefited from the administration of levodopa and apomorphine. A small randomized clinical trial of the synthetic cannabinoid, nabilone, in seven patients with Parkinson's disease found that the treatment reduced levodopa-induced dyskinesia in these patients[252].

4.6.1.4 Tourette's syndrome.

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[247] M Glass.The role of cannabinoids in neurodegenerative diseases. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25: 743-65

[248] P Consroe, R Sandyk, SR Snider. Open label evaluation of cannabidiol in dystonic movement disorders. Int J Neurosci. 1986; 30: 277-82.

[249] SH Fox, M Kellett, AP Moore, AR Crossman, JM Brotchie. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Mov Disord. 2002; 17: 145-149.

[250] P Consroe, J Laguna, J Allender, S Snider, L Stern, R Sandyk, K Kennedy, K Schram. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav. 1991; 40: 701-8.

[251] JP Frankel, A Hughes, AJ Lees, GM Stern. Marijuana for parkinsonian tremor. J Neurol Neurosurg Psychiatry. 1990; 53: 436.

[252] KA Sieradzan, SH Fox, M Hill, JP Dick, AR Crossman, JM Brotchie. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology. 2001; 57: 2108-11.

Clinical reports consisting of four case histories suggest that smoked marihuana use can reduce tics in Tourette's patients[253]. In one report of 3 patients, it is hypothesized that beneficial effects of marihuana might have been due to anxiety-reducing properties of marihuana rather than to a specific anti-tic effect[254]. A randomized, double-blind, placebo controlled trial of single oral doses of THC (5, 7.5 or 10 mg) has been carried out in 12 patients with Tourette's syndrome. Objective ratings showed plasma concentration-related improvements in control of tics and obsessive-compulsive behaviour, with no serious side effects; although transient, mild side-effects were noted in five patients[255]. A related study showed that in contrast to healthy marihuana users, single does of THC (5-10 mg) caused no cognitive impairment measured by objective tests in 12 patients with Tourette's syndrome[256].

4.6.2 Glaucoma

The high intraocular pressure (IOP) of glaucoma can be reduced by marihuana (oral or smoked) and there are a few reports from treatment of glaucoma patients[257]. A pilot open trial[258] in 11 glaucoma patients with 1, 2 and 4% THC smoked marihuana and 15 mg oral THC found a 30% drop in IOP with 7 patients and no effect with the other 4. A survey led to 20 opthalmologists wishing to take part in a compassionate access program to use cannabis to treat glaucoma patients[259]. However, only nine patients were enrolled to be administered either orally administered oral THC or inhaled marihuana in addition to their existing medications Although an initial decrease in intraocular pressure was observed in all patients, the decreases in intraocular pressure were not sustained and for various reasons, all patients elected to discontinue treatment within 1 to 9 months.There is an anecdotal report of 2 glaucoma patients who had relief from IOP and alleviation of symptoms with smoked marihuana[260].

A double-blind, placebo-controlled trial of 2% THC smoked marihuana in 18 patients with heterogeneous glaucomas showed a significant reduction in IOP, but this was accompanied by unacceptable side-effects including hypotension,

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[253] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999, p4.32.

[254] R Sandyk, G Awerbuch. Marijuana and Tourette's syndrome. J Clin Psychopharmacol. 1988; 8: 444-445.

[255] KR Muller-Vahl, U Schneider, A Koblenz, M Jobges, H Kolbe, T Daldrup, HM Emrich. Treatment of Tourette's syndrome with Delta 9-THC: a randomized crossover trial. Pharmacopsychiatry. 2002; 35: 57-61.

[256] KR Muller-Vahl, A Koblenz, M Jobges, H Kolbe, HM Emrich, U Schneider. Influence of treatment of Tourette's syndrome with delta-9-THC on neuropsychological performance. Pharmacopsychiatry. 2001; 34: 19-24.

[257] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p55.

[258] RS Hepler, IM Frank, R Petrus. Ocular effects of marijuana smoking. In eds. M C Braude, S Szara, The Pharmacology of marijuana. Raven Press, New York, 1976, pp815-824

[259] AJ Flach. Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. Trans Am Ophthalmol Soc 2002;100:215-22

[260] L Grinspoon, JB Bakalar Marijuana the forbidden medicine, Yale University Press, Newhaven, 1993.

palpitations and psychotropic effects[261]. Another study of more than 300 subjects[262] with both normal and raised IOP reported that marihuana causes an average reduction of 25% in IOP that lasts for 3 to 4 h. However, to prevent retinal and optic disc damage in glaucoma, the IOP must be reduced 24 h a day, so that patients would have to smoke 6 to 10 times a day to maintain continuous IOP reduction. One reviewer remarks[263] that "smoking of marijuana plant material for the reduction of elevated IOP in glaucoma is ill-advised, given its toxicological profile." However it is also noted therein, and by other specialists[264] that research with cannabinoids including the discovery of ocular cannabinoid receptors could lead to improved agents for glaucoma treatment.

4.6.3 Bronchial asthma

While cannabinoids are bronchodilators, there have been very few studies of the bronchodilator effect in asthmatic patients. A double-blind, placebo-controlled study of smoked marihuana (2% THC), oral THC (15mg) and isoprenaline (0.5%) in 14 asthmatic subjects showed reversal of experimental bronchospasm by bronchodilation which was almost equivalent between the marihuana and isoprenaline[265]. However, tolerance to this effect developed after several weeks.[266]

Another single-blind investigation of smoked marihuana (0.9 and 1.9% THC) found that it caused significant and prolonged bronchodilation, but tachycardia occurred with the higher dose[267]. It is clear that smoked marihuana is not suitable for chronic use in asthma because of bronchial irritation from various components of smoke. Thus, the BMA notes that smoking cannabis in asthma is "not a therapeutic option, because of the adverse effects of smoke"[268].

4.6.4 Hypertension

Cannabinoids cause postural hypotension, but tolerance to the cardiovascular effects develops rapidly and together with adverse effects, this would preclude their consideration as a treatment for long-term use in hypertension[269].

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[261] JC Merritt, WJ Crawford, PC Alexander, AL Anduze, SS Gelbart. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980; 87: 222-8.

[262] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p165.

[263] K Green. Marijuana smoking vs cannabinoids for glaucoma therapy. Arch Ophthalmol 1998; 111: 1433-1437.

[264] T Jarvinen, DW Pate, K Laine. Cannabinoids in the treatment of glaucoma. Pharmacol Ther 2002; 95: 203-220.

[265] DP Tashkin, BNJ Shapiro, IM Frank. Acute effects of marihuana on airway dynamics in spontaneous and experimentally produced bronchial asthma. In The pharmacology of marihuana. eds. MC Braude, S Szara, Raven Press , New York, 1976.

[266] DP Tashkin, BJ Shapiro, EY Lee, CE Harper. Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. New Eng J Med, 1976; 294: 125-129

[267] L Vachon, P Mikus, W Morrisey, M Fitzgerald, E Gaenser. Bronchial effects of marihuana smoke in asthma. In The pharmacology of marihuana. eds. MC Braude, S Szara, Raven Press , New York, 1976.

[268] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 60.

[269] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997.p 64

4.6.5 Mood disorders

Cannabis has been advocated as a treatment for anxiety, depression, sleep disorders and alcohol and opiate withdrawal symptoms [270]. Most of this use is anecdotal and occurred before modern psychotherapeutic agents became available. One anecdote concerns relief of depression by smoking marihuana, with much faster mood alteration than from amitriptyline, a conventional antidepressant that usually takes some weeks to take effect [271]. Trials for treatment of chemotherapy-induced nausea with cannabinoids have mentioned some anti-depressant advantages[272]. However, these are offset by the potential for severe psychological side effects.

Anecdotal information and some animal studies suggest that cannabinoids may be useful in treatment of opiate withdrawal, but there are no clinical studies to support this indication[273].

4.6.6 Alzheimer's disease

Two possible indications for cannabinoid treatment in Alzheimer's are to stimulate appetite (reverse food refusal) and improve behaviour. Although oral THC (dronabinol) has been investigated in 11 patients and showed efficacy[274], there are concerns about the known THC effects on memory of healthy adults in this condition in which memory is already diminishing. There are also obvious concerns about the fire hazards of smoking marihuana in such a group of impaired patients.

5.0 Contraindications

Marihuana is contraindicated in any patient who has a history of hypersensitivity to any cannabinoid or to smoking. Marihuana should not be used in patients with a history of psychotic disorders, particularly schizophrenia.

6.0 Warnings

The dose of marihuana is difficult to estimate and is affected by source of plant material, its processing and by the different smoking procedures. These include depth of inhalation and breath-holding and number and frequency of puffs as well as how much of the cigarette is smoked. Smoking should be gradual and should cease if the patient begins to feel disoriented or agitated. Experienced smokers are able to "titrate" their dose from the

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[270] LL Iversen. The science of marijuana. Oxford University Press, Oxford New York, 2000 p 172

[271] L Grinspoon, JB Bakalar Marijuana the forbidden medicine, Yale University Press, Newhaven, 1993.

[272] W Regelson, JR Butler, J Schulz, T Kirk, L Peek, ML Green, MO Zalis. Delta-9 THC as an effective antidepressant and appetite stimulating agent in advanced cancer patients. In The pharmacology of marihuana. eds. MC Braude, S Szara, Raven press , New York, 1976.

[273] British Medical Association. Therapeutic uses of cannabis. Harwood Academic Publishers, Amsterdam, 1997. p 64.

[274] L Volicer, M Stelly, J Morris, J McLaughlin, BJ Volicer. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 1997; 12: 913-9.

rapid intake, but naïve smokers should take great care and be supervised.

Marihuana can produce physical and psychological dependence and has the potential for abuse. The drug has complex effects in the central nervous system. These can result in decrease in cognitive ability and memory, mood changes, alteration in the perception of reality and decrease in the ability to control impulses. Because of the ability to interfere with mental state, patients should be under supervision when dosed.

Any patient experiencing a psychotic reaction under the influence of the drug, should stop taking the drug immediately and be kept under observation until normal mental state is regained.

Occupational hazards: Patients using marihuana should be warned not to drive or perform hazardous tasks such as operating heavy machinery because impairment of mental alertness and physical coordination may decrease their ability to perform such tasks. Such impairment can last for over 24 hours after using due to the long half-life of THC.

Pregnancy Use of marihuana during pregnancy should be avoided as there is evidence of long term development problems to children of women who used cannabis recreationally.

Lactation: Cannabinoids are excreted in human milk and may be absorbed by the nursing baby. Because of potential risks to the child, nursing mothers should not use marihuana.

7.0 Precautions

7.1 General

The risk/benefit ratio of marihuana should be carefully evaluated in patients with the following medical conditions, because of individual variation in response and tolerance to its effects as well as the difficulty in dosing noted in section 3.0:

- Marihuana should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia.

- Smoked marihuana is not recommended in patients with respiratory insufficiency such as asthma or chronic obstructive pulmonary disease.

- Marihuana should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse marihuana, which itself, is a frequently abused substance.

- Patients with mania, depression, or schizophrenia should be under careful psychiatric monitoring if marihuana is taken, because it may exacerbate these illnesses.

- Marihuana should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.

Patients should be advised about likely negative effects on memory and be advised to report any mental or behavioral changes that occur after using marihuana.

7.2 Dependence and withdrawal

Tolerance, psychological and physical dependence may occur with prolonged repetitive use of marihuana. Tolerance to cardiovascular effects occurs quickly, but the dependence is slower to develop and appears more likely with higher, more frequent dosing.

7.3 Special populations

Marihuana should be used with caution in pregnant, pediatric and elderly patients, because there is insufficient knowledge about its use in these patient populations and the potential for harm is likely to outweigh benefits.

7.4 Drug Interactions

THC and CBD are metabolized by the cytochrome P_{450} system and *in vitro* human microsomal studies have suggested a potential for interaction with other drugs. CBD has been shown to inhibit formation of THC metabolites catalyzed by CYP 3A with less effect on CYP 2C9. For this reason there is concern that in patients undergoing multiple drug therapy, such as treatment of AIDS or cancer, clinically significant drug interactions might occur. However, both with dronabinol and smoked marihuana clinically significant interactions have not been detected. Protein binding is another possible source of interaction and patients exposed to marihuana should be monitored for a change in dosing requirements if they are taking other drugs that are highly protein-bound.

7.5 Drug screening tests

Patients should be aware that because of the long half-life of elimination of cannabinoids and their metabolites, drug screening tests can be positive long after using marihuana (weeks with some tests).

8.0 Adverse effects

This section includes known cannabis-related effects (*e.g.*, cardiac) and also effects related to smoking (*e.g.*, respiratory).

8.1 Carcinogenesis, mutagenesis and respiratory tract

While THC (dronabinol) was negative in the Ames test, carcinogenicity studies have not been reported[275]. There is much more information on potential carcinogenicity from long-term marihuana smoking. More recent work[276] suggests that CB1 receptors under certain conditions may mediate inhibition of tumor cell growth as well as other cellular events and requires further investigation[277].

There are problems with epidemiology studies of cannabis smokers, since it is difficult to eliminate the confounding effects of tobacco smoking, but the only epidemiological study in relatively young health maintenance organization (HMO) clients found an increased number of men with prostate cancer in smokers of cannabis and other non-tobacco materials. In this study, limited by the demographics of the HMO clientel and the low marihuana exposures, there were no other associations found between marihuana use and other cancers[278]. A case control study[279] compared 173 previously untreated cases with pathologically confirmed diagnoses of squamous cell carcinoma of the head and neck and 176 cancer-free controls. Controlling for age, sex, race, education, alcohol consumption, pack-years of cigarette smoking, and passive smoking, the risk of squamous cell carcinoma of the head and neck was increased with marijuana use and suggested that marijuana use may increase the risk of head and neck cancer with a strong dose-response pattern. The risk was increased 36-fold in those using both marihuana and tobacco compared to non-smoking controls. There has also been a rise in the number of cancers of the respiratory and digestive systems that are rare in young patients and are attributed to marihuana smoking[280, 281]. In addition there are many cellular and molecular studies that provide strong evidence that smoked marihuana is carcinogenic[282]. Cannabis smoke has been shown to have a depressant effect on normal cell function and on cell division in cell cultures. When human lung cultures were exposed daily to 4 puffs of 25 ml smoke from cannabis, for up to two months, abnormalities in mitosis, increased variation in DNA content and chromosome number were observed. Early changes were less marked for cannabis than for tobacco smoke. Later increases in DNA content were similar for both smoke types. In similarly treated hamster lung cultures, enhanced

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[275] Marinol® U.S monograph Unimed Pharmaceuticals Inc. http://www.marinol.com/pdf/Marinol.pdf Marinol®

[276] V Di Marzo, L De Petrocellis, F Fezza, A Ligresti, T Bisogno. Anadamide receptors..Prostaglandins Leukot Essent fatty Acids, 2002, 66: 377-391.

[277] M Bifulco, V Di Marzo. Targeting the endocannabinoid system in cancer therapy: a call for further research. Nat Med. 2002;8: 547-550.

[278] S Sidney, CP Quesenberry Jr, GD Friedman, IS Tekawa. Marijuana use and cancer incidence (California, United States). Cancer Causes Control. 1997; 8: 722-728.

[279] ZF Zhang, H Morgenstern, MR Spitz, DP Tashkin, GP Yu, JR Marshall, TC Hsu, SP.Schantz Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 1999; 8: 1071-8.

[280] G Hyman. Marihuana smoking, a possible carcinogen or co-carcinogen. " In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999 pp 289-290.

[281] W Hall, N Solowij.Adverse effects of cannabis. Lancet. 1998; 352: 1611-1616.

[282] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p3.41

transformation of malignant cells was noted, comparable with exposure to tobacco smoke[283].

Epidemiological studies have found mild pulmonary function changes in heavy cannabis smokers, including reduction of forced expiratory volume in 1 second (FEV_1), increase in airway resistance and decrease in airway conductance[284,285,286]. Heavy chronic smokers presented with symptoms of bronchitis, including wheezing, production of phlegm and chronic cough and it may be a risk factor for chronic obstructive pulmonary disease in later life [287,288]. All changes were most evident in heavy chronic users, defined as those who smoked more than 3 joints per day for 25 years[289, 290]. Histopathology results also showed damage to the airway cel1s[291, 292, 293] including squamous metaplasia, goblet cell hyperplasia and cellular disorganization. However, not all studies found the changes to be significant[294]. The effects on the respiratory tract defence system may increase the risk of infection in chronic users[295]. Thus although additional epidemiological studies are required to determine the potential causal relationship between marijuana use and the development of respiratory infection and/or cancer, evidence is mounting that habitual smoking of marijuana has a number of adverse effects on the respiratory and immune systems (see below) that may be clinically relevant[296].

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[283] C Leuchtenberger, R Leuchtenberger. Cytological and cytochemical studies of the effects of fresh marihuana cigarette smoke on growth and DNA metabolism of animal and human lung cultures. In: MC Braude, S Szara, editors. The Pharmacology of Marihuana. New York: Raven Press; 1976. p. 595-612.

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[286] DP Tashkin, AH Coulson, VA Clark, M Simmons, LB Bourque, S Duann, GH Spivey, H Gong. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis. 1987; 135 209-216.

[287] W Hall, N Solowij.Adverse effects of cannabis. Lancet. 1998; 352: 1611-1616.

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[289] S Sidney, CP Quesenberry Jr, GD Friedman, IS Tekawa. Marijuana use and cancer incidence (California, United States). Cancer Causes Control. 1997; 8: 722-728.

[290] DP Tashkin . Marihuana and the lung. " In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999, p 279-287.

[291] G Hyman. Marihuana smoking, a possible carcinogen or co-carcinogen. " In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999 pp 289-290.

[292] SEG Fliegel, MD Roth, EC Kleerup, SH Barsky, M Simmons, DP Tashkin. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana and/or tobacco. Chest, 1997; 112: 319-326.

[293] MD Roth, A Arora, SH Barsky, EC Kleerup, M Simmons, DP Tashkin. Airway inflammation in young marijuana and tobacco smokers. Am.J.Respir.Crit Care Med.1998;157(3 Pt 1):928-937.

[294] MP Sherman, MD Roth, H Gong, Jr., DP Tashkin. Marijuana smoking, pulmonary function, and lung macrophage oxidant release. Pharmacol.Biochem.Behav. 1991; 40:663-669.

[295] DW Denning, SE Follansbee, M Scolaro, S Norris, H Edelstein, DA Stevens. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med. 1991; 324: 654-662.

[296] DR Tashkin, GC Baldwin, T Sarafian, S Dubinett, MD Roth. Respiratory and immunologic consequences of marijuana smoking. J Clin Pharmacol 2002;42(11 Suppl): 71S-81S

8.2 Immune system

The effects of marihuana smoking on the immune system are inconclusive. Rodent studies with cannabis have shown decreasing resistance to infection by impairment of cell-mediated and humoral immunity[297]. Because of the high dosing in animals, the relevance to human immunity is unclear[298, 299] .However, among patients suffering from AIDS, the increased mortality and reports of opportunistic bacterial and fungal infections associated with marihuana use cause concern. Reviews suggest[300], [301] that such patients may be exposed to more pathogens or that the immune system is suppressed by marihuana[302]. However, there has only been one short clinical study. This was a randomized, prospective, controlled, 21 day trial completed in 62 HIV-infected adults patients who were taking protease inhibitor containing highly active antiretroviral treatments[303]. Standard immunochemistry tests in this group compared the effects of use of marijuana cigarettes (3.95% THC, n=20), dronabinol (2.5 mg, n=22), and oral placebo (n=20). No evidence of detrimental effects on immune parameters by cannabinoid treratment was found.

8.3 Reproductive and endocrine systems

Animal studies with THC and cannabis in reproductive systems are usually acute or short term observations, and have shown inhibition of reproductive functions. In both male and female animals THC suppresses release of hormones, including luteinising hormone, lowering testosterone secretion and disrupting the ovulatory cycle. These effects appear to be parallelled in the short-term with humans using marihuana. THC interferes with embryo implantation and lowers birth weight in animals[304, 305] but the relevance of these short term acute experiments to humans is not clear[306]. Results of human epidemiological

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[297] AE Munson, KO Fehr. Immunological effects of cannabis. In eds. KO Fehr, H Kalant, Cannabis and health hazards, Addiction Research Foundation, Toronto, 1983.
[298] TW Klein, H Friedman, S Specter. Marijuana, immunity and infection. J.Neuroimmunol. 1998; 83: 102-115.
[299] W Hall, N Solowij. Adverse effects of cannabis. Lancet. 1998; 352: 1611-1616.
[300] G. Cabral Marijuana and cannabinoids: effects on infections, immunity, and AIDS. J. Cannabis Ther, 2001; 1:61-85
[301] T. Klein Cannabinoids and the immune system. Pain Res Management, 2001; 6:95-101.
[302] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p3.39.
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[304] E Bloch. Effects of marihuana and cannabinoids on reproduction, endocrine function , development and chromosomes. In eds. KOFehr, H Kalant, Cannabis and health hazards, Addiction Research Foundation, Toronto, 1983.
[305] EL Abel. Effects of prenatal exposure to cannabinoids. In ed. TM Pinkert Current research on the consequences of maternal drug abuse. NIDA Research Monograph, no 59, U.S. Department of Health and Human Services, Washington, DC, 1985.
[306] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 3.45.

studies have been conflicting; some report reduced birth weight[307] and others no effect on birth weight[308] among women who smoked cannabis during pregnancy. There appears to be some long-term effects on development of children born to mothers who used marihuana during pregnancy. Two longitudinal investigations over 20 years[309], confirmed by a third[310], suggest that such *in utero* exposure impacts negatively on attentional behavior and visual analysis/hypothesis testing but not on standardized derived IQ scores. In later years these behavioral effects have a negative influence on aspects of executive function. Also, frequent maternal cannabis use may be a weak risk factor for sudden infant death syndrome (SIDS). In a recent study[311] the SIDS odds ratio for more than weekly maternal cannabis use since the infant's birth was 2.23 (95% CI = 1.39, 3.57) compared to non-users; and the multivariate odds ratio was 1.55 (95% CI = 0.87, 2.75) but further research is required.

There is little information concerning transfer of cannabinoids and their metabolites in human milk[312,313] . However, in habitual maternal users of marihuana the above influences in development and behaviour would also be relevant. In a case-control study[314] 68 infants were exposed to marihuana *via* the mother's milk compared to 68 infants and matched to the marihuana-exposed infants on pre- and postpartum maternal alcohol and tobacco use. Exposure to marihuana from the mother's milk, during the first month postpartum, appeared to be associated with a decrease in infant motor development at one year of age.

8.4 Cardiovascular effects

The most consistent acute physiological effect of smoking marihuana is dose-related tachycardia[315]. While cardiovascular changes have not usually been a problem for healthy young users, the tachycardia induced by cannabis smoking may be problematic to those

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[307] B Zuckerman, DA Frank, R Hingson, H Amaro, SM Levenson, H Kayne, S Parker, R Vinci, K Aboagye, LE,Fried. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med. 1989 ; 320: 762-8.

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[311] RK Scragg, EA Mitchell, RP Ford, JM Thompson, BJ Taylor, AW Stewart. Maternal cannabis use in the sudden death syndrome. Acta Paediatr 2001; 90: 57-60.

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[314]SJ Astley, RE.Little Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol 1990; 12: 161-168.

[315] R Trouve, G Nahas. Cardiovascular effects of marihuana and cannabinoids. " In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999, pp 291-304.

already suffering from cardiac disorders or angina[316]. It was found that inhalation of cannabis smoke reduces the amount of exercise required to cause an attack by 50%[317]. Recently, marihuana has been associated with an increased relative risk of non-fatal myocardial infarction in the first hour following smoking[318]. This may be due to increasing myocardial oxygen demand from the increase in heart rate following cannabis use. However, other drug use could confound reports [319]. One recent study reported six cases of possible acute cardiovascular deaths in young adults where post-mortem toxicological blood analysis showed presence of cannabis alone, indicating recent use [320]. Other recent publications have reported cases of paroxysmal atrial fibrillation[321], transient cerebral ischemic episodes[322] and sudden cardiac death[323] occurring shortly after exposure to smoked or oral cannabis. The affected individuals were young adults who may have had pre-existing cardiovascular problems.

Cannabis is known to cause postural hypotension immediately after smoking [324]. It also causes peripheral vasodilatation, which can impact on body temperature perception and is involved in characteristic conjunctival reddening. The mechanisms for those effects on the autonomic nervous system are not understood[325].

Chronic marihuana smoking appears to induce tolerance to the cardiac accelerating effect and, in fact, after about eight days of constant dosing with equivalent of 10 mg of THC per day (equivalent to 100 mg of marihuana containing 10% THC), bradycardia with hypotension (decrease in supine blood pressure) was observed [326].

Patients with normal cardiac function could therefore take marihuana without immediate concern about effects on the heart, but THC and smoked marihuana poses health risks to people with cardiovascular disease because of the consequences of the resulting

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[316] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 3.44.

[317] WS Aronow, J Cassidy. Effect of marihuana and placebo-marihuana smoking on angina pectoris. N.Engl.J.Med. 1974; 291: 65-67.

[318] MA Mittleman, RA Lewis, M Maclure, JB Sherwood, JE Muller. Triggering myocardial infarction by marijuana. Circulation. 2001; 103:2805-2809.

[319] LE Hollister. Health aspects of cannabis revisited. Int J Neuropsychopharmacol. 1998; 1: 71-80

[320] L Bachs, H. Morland Acute cardiovascular fatalities following cannabis use. Forensic Sci Int. 2001; 124: 200-3

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[325] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p 3.44

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increased cardiac work, increased catecholamine levels, carboxyhemoglobin, and postural hypotension [327],[328],[329].

AIDS patients may be at risk of cardiovascular effects from interactions of their antiviral drugs, such as ritonavir, which has been shown to cause plasma lipid abnormalities that increase risk of cardiovascular events [330]. As this patient population may use cannabis for weight gain or other amelioration of symptoms, the additional cardiovascular effects from the marihuana should be considered in risk assessment.

8.5 Central Nervous System

The acute effects on the brain of smoking marihuana are described under the Clinical Pharmacology (section 2.0) and include the "high", the potential for adverse mood reactions such as anxiety and paranoia in naïve smokers (especially with potent cigarettes) and cognitive and behavioural effects. This section will provide more detailed commentary on the CNS effects and potential damage from chronic use.

According to the Marinol® (oral THC) product monograph, the most commonly encountered CNS events in controlled clinical trials were drowsiness, dizziness and transient impairment of sensory and perceptual functions[331]. Psychotropic effects were observed in most patients; these included the "high" (easy laughing, elation, heightened awareness) in 24% of the THC group. Other effects at about 5% in the THC and absent in the placebo group were weakness or sluggishness, hallucinations, memory lapse and ataxia. Other events (and percentages) reported were dry mouth, parasthesia, visual distortions (all at 3%), paranoia, depersonalization (each 2%) and disorientation with confusion (1%).

Although there have been many experiments with animals[332] the information from humans has not shown that chronic use of cannabis results in brain damage either by brain-scanning techniques[333] (tomography) or from *post-mortem* histology [334] . However, these negative findings do not preclude more subtle changes[335].

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[327] R Trouve, G Nahas. Cardiovascular effects of marihuana and cannabinoids. In Marihuana and Medicine, Assessing the science base. National Academy Press, Washington, D.C., 1999 pp 291-304

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[331]Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[332] N Solowij. Long-term effects of cannabis on the central nervous system. In " the Health effects of cannabis",1999, pp 195-265.

[333]J Hannerz, T Hindmarsh. Neurological and neuroradiological examination of chronic cannabis smokers. Ann Neurol. 1983; 13: 207-210.

[334]M Glass, M Dragunow, RL Faull. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience. 1997; 77: 299-318.

[335] N Solowij. Long-term effects of cannabis on the central nervous system. In " the Health effects of cannabis",1999, pp 195-265.

8.5.1 Cognition

Marihuana impairs cognition involving short-term memory, attention and concentration. Research has examined the effect of cannabis on both short term and long term memory retrieval, including associative and semantic processes. The digit span task has been used to estimate the effects of cannabis on recent memory, but results have been inconsistent. Such differences may be due to the dosage used (% THC), the smoking procedure or whether the digit span task assesses forward or backward recall[336] . Also methodological difficulties have contributed to difficulties in assessing the effects of chronic use[337]. However, overall, studies suggest that chronic users of marihuana suffer varying degrees of cognitive impairment that can be long lasting[338]. Cannabis intoxication significantly impairs the ability to learn and recall word lists or short stories. Recent studies with 51 long-term marihuana smokers (mean 24 years) compared to non-smoker and short term user controls, have confirmed that deficits in attention and memory occur with heavy cannabis users and these continue beyond the period of intoxication and are cumulative with longer periods of use[339]. Nine standard neuropsychological tests assessed attention, memory, and executive functioning, and were administered before and after abstinence[340]. One problem with that study is that "period of abstinence" was median 17 hours and is probably insufficient time, in reference to the long half-life of elimination of cannabinoids and their metabolites.

8.5.2 Psychomotor Performance

The acute effects of cannabis exposure affect psychomotor performance and patients must be warned not to drive after smoking marihuana. The period of time to abstain from operating complex machinery depends on the dose, the disease being treated and the patient's age and even gender. It is evident that individuals are affected differently by prolonged exposure to marihuana and although not fully researched there is some evidence of greater effects on adolescents, but the discrimination from the normal effects of aging on cognition and performance have not been fully researched[341]. Performance impairment appears to be less among people who are heavy users of cannabis compared to occasional users[342] . It has been suggested that, unlike alcohol, cannabis users are aware of their level of intoxication and compensate

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[336]SJ Heishman, ML Stitzer, JE Yingling. Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. Pharmacol.Biochem.Behav. 1989; 34: 173-179.

[337]HG Pope Jr, AJ Gruber, D Yurgelun-Todd. The residual neuropsychological effects of cannabis: the current status of research. Drug Alcohol Depend. 1995; 8: 25-34.

[338] LE Hollister. Health aspects of cannabis: revisited. .Int J Neuropsychopharmcol. 1998 Jul;1(1):71-80.

[339]N Solowij, R Stephens, RA Roffman, T Babor. Does marijuana use cause long-term cognitive deficits? JAMA. 2002; 287: 2653-2654.

[340]N Solowij, RS Stephens, RA Roffman, T Babor, R Kadden, M Miller, K Christiansen, B McRee, J Vendetti. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA. 2002 ; 287: 1123-1131.

[341]N Solowij. Long-term effects of cannabis on the central nervous system. In " the Health effects of cannabis",1999, pp 195-265.

[342] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C, 1999 p 3.8

to become hyper-cautious, resulting in decrease of speed, decreased frequency of overtaking as well as an increase in following distance[343]. Others disagree with this assertion[344]. A series of tests on pilots demonstrated that in simulation of the very complex tasks of flight there were carryover effects on performance of pilots 24 hours after smoking marihuana and that they were unaware of these impairments [345]. Some reports suggest that there may be lingering impairments [346].

8.5.3 Behavioural effects

There are a number of behavioral subtopics to be addressed including psychiatric disorders, addiction, dependence, tolerance and "amotivational syndrome". As with so much of the literature on effects of marihuana, there is little consensus.

8.5.3.1 Psychiatric disorders.

It is noted in the Marinol® (dronabinol, oral THC) product monograph[347] that this drug should be used with caution and careful psychiatric monitoring in patients with mania, depression , or schizophrenia because Marinol® may exacerbate these illnesses. This reflects the IOM report[348] and also the knowledge that psychiatric disorders are associated with substance dependence and are risk factors for drug abuse.

Acute toxic reactions such as nausea, anxiety, paranoia and disorientation often occur in naïve marihuana smokers but are uncommon in regular users [349]. The triggering of psychosis by marihuana has not been definitively established, but it appears that cannabis is frequently used by psychotic patients[350]. Other reviewers conclude that heavy cannabis smoking, and even lighter use in susceptible individuals, can produce an acute psychosis including anxiety, agitation, amnesia, delusions, hallucinations and hypomanic symptoms[351].

8.5.3.2 Schizophrenia

It has been considered overall that marihuana use does not cause schizophrenia. However, self-reported use of cannabis in childhood has been associated with an

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[343]DH Gieringer. Marijuana, driving, and accident safety. J Psychoactive Drugs. 1988; 20: 93-101

[344]H Moskowitz. Marihuana and driving. Accid Anal Prev. 1985; 17: 323-345.

[345] VO Leirer, JA Tesavage, DG Morrow. Marijuana carry-over effects on aircraft pilot performance. Aviat Space Envrion Med. 1991;62: 221-7

[346] N Solowij. Long-term effects of cannabis on the central nervous system. In " the Health effects of cannabis",1999, pp 195-265.

[347] Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003.

[348] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 pp 3.23 and 3.29.

[349]R Noyes Jr, SF Brunk, DA Baram, A Canter. Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol. 1975; 15: 139-43

[350] LE Hollister. Health aspects of cannabis: revisited. .Int J Neuropsychopharmcol. 1998 Jul;1(1):71-80.

[351] Australian Commonwealth government, Department of Health and Ageing, National Drug Strategy, Monograph Series No.44 The health and psychological effects of cannabis use. National Drug and Alcohol Research Centre, University of New South Wales. Wayne Hall, Louisa Degenhardt, Michael Lynskey. 1994, p 90-92

increased risk of developing schizophrenia and this risk was related to frequency of marihuana exposure[352]. Recent findings[353] in a cohort of over 1000 children, followed to age 26 from birth, showed threefold increased risk of psychotic disorders in cannabis users and suggest that cannabis exposure among psychologically vulnerable adolescents should be strongly discouraged. Heavy marihuana use can aggravate symptoms and cause more relapses[354 355]. Follow-up studies confirm the increased risk of poor prognosis in psychosis for those using marihuana[356,357]. Individuals with schizophrenia or with a family history of this disorder are likely to be at greater risk of suffering adverse psychiatric effects from marihuana[358].

8.5.3.3 Amotivational syndrome

This syndrome is used to describe young people who show little interest in school, work or other goal-oriented activity as well as withdrawing from social activities. While it is an ill-defined condition, this is a common feature of chronic intoxication with many different psychoactive drugs and when the chronic intoxication is treated or "cured" the behaviour improves. There is no convincing evidence to show a casual relationship between marihuana smoking and such behavioural characteristics.[359].

8.5.3.4 Dependence, tolerance and "addiction"

These are among the most controversial topics in marihuana research, particularly concerning the existence of a cannabis withdrawal symptom[360 361] . Most of the dependence information has been developed from the recreational use of

[352]S Zammit, P Allebeck, S Andreasson, I Lundberg, G Lewis. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 2002; 325: 1199-1201

[353]L Arseneault, M Cannon, R Poulton, R Murray, A Caspi, T E Moffitt.
Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002; 325: 1212-1213.

[354]P Allebeck**.** Cannabis and psychiatric syndrome. " In Marihuana and Medicine. Eds. GG Nahas, KM Sutin, D Harvey, S Agurell, Humana Press, Totowa, N.J., 1999, pp 665-669

[355] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p3.29**.**

[356]D Caspari. Cannabis and schizophrenia: results of a follow-up study. Eur Arch Psychiatry Clin Neurosci 1999;249:45-49

[357]J van Os, M Bak, M Hanssen, RV Bijl, R de Graaf, H Verdoux. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol 2002;156: 319-327

[358]A Johns. Psychiatric effects of cannabis. Br J Psychiatry. 2001; 178: 116-122.

[359] National Academy of Sciences, Institute of Medicine (IOM) Marihuana and medicine: Assessing the science base. National Academy Press, Washington, D.C., 1999 p3.31.

[360] World Health Organization. Cannabis: a health perspective and research agenda, 1997 http://www.who.int/substance_abuse/docs/cannabis.pdf

[361] NT Smith. A review of the published literature into cannabis withdrawal symptoms in human users. Addiction. 2002; 97: 621-632.

marihuana and does not seem to have been studied in patients who use the drug chronically for its potential therapeutic effects[362].

While commonly applied by the general public, because of imprecision, the term "addiction" which designates substance dependence, is now less favoured by experts. Reviews do not always adhere to this usage and the IOM report defines addiction, craving, physiological dependence, reinforcement, substance dependence (full definition of addiction) tolerance and withdrawal[363]. Although not without critics, The DSM-IV criteria[364] for assessing substance dependence are widely used.

Tolerance to most of the effects of marihuana can develop after a few doses and it also disappears rapidly[365]. In normal subjects tolerance develops to mood, intraocular pressure, EEG changes, psychomotor performance, antiemetic effects[366] as well as to cardiovascular effects[367]. The dynamics of tolerance differs for different effects[368]. Tolerance to some of the cannabis effects develops both when THC is administered orally (30 mg four times a day) and when a roughly equivalent dose was given by smoking[369] (3.1% cigarette, 5 x 10 second puffs). Both groups became tolerant to the "high", but there was no diminution of the appetite stimulating effect from either route of administration.

There is evidence that cannabis dependence occurs with chronic heavy recreational use: some individuals report problems in controlling such use despite personal difficulties[370], [371]. However, dependence is unlikely to present problems with cannabis used in therapeutic circumstances although withdrawal effects may

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be uncomfortable[372]. These include restlessness, anxiety, mild agitation, irritability, tremor, insomnia and EEG/ sleep disturbance, nausea, diarrhea and cramping. Withdrawal has been studied in subjects, including adolescents who smoked marihuana recreationally[373]. These effects are considered mild compared to the physical "syndromes" experienced with alcohol or opiate withdrawal[374] and the pattern of withdrawal is less clear than for these drugs[375].

9.0 Overdose/Toxicity

Animal toxicology reports record that mice, rats and monkeys can tolerate 1 gram THC/kg of body weight, equivalent to 5,000 times the dose producing a "high" in humans. The LD_{50} is estimated as around 1: 20,000 to 1:40, 000[376]. However, marihuana is not a completely benign agent and it has a variety of physiological effects, but aside from the hazards consequent to smoking the adverse effects are within the range tolerated for other medications[377]. Cannabis often produces unwanted effects, typically dizziness, sedation, intoxication, clumsiness, dry mouth, lowered blood pressure or increased heart rate[378]. The rare acute complications (such as panic attacks, psychosis, convulsions etc...) that present to the Emergency Department can be managed with conservative measures[379]. As is stated for overdose with Marinol®[380], signs and symptoms with smoked marihuana are an extension of the psychotomimetic and physiologic effects of THC. If disturbing psychiatric symptoms occur at the prescribed dosage, the patient should be closely observed in a quiet environment and supportive measures, including reassurance, should be used.

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