



Information for Health Care Professionals

Marihuana (marijuana, cannabis)

dried plant for administration by ingestion or other means
Psychoactive agent

This document has been prepared by the Controlled Substances and Tobacco Directorate at Health Canada 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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1.0 Chemistry

1.1 Composition

Marihuana (Marijuana) is the common name for *Cannabis*, a hemp plant that grows throughout temperate and tropical climates (1). Although the leaves and flowering tops of *Cannabis* plants yield more than 60 different phyto-cannabinoids, the major active components are delta-9-tetrahydrocannabinol (Δ^9 -THC, THC), cannabinalol (CBN) and cannabidiol (CBD) (2). Other cannabinoids found in marihuana include cannabigerol (CBG), cannabichromene (CBC) and many others (3). In the living plant, these phytocannabinoids exist primarily as inactive monocarboxylic acids; heating triggers their decarboxylation and results in biological activation (4,5).

Δ^9 -THC is the best studied cannabinoid and is responsible for most of the physical and psychotropic effects of cannabis (6). Other cannabinoids (such as CBD, CBC, CBG) are present in lesser amounts in the plant and have little if any psychotropic properties (6). It is reasonable to consider about 10% (range 1-30%) as an average for THC content in cannabis found on the illicit market in Canada (internal communication). The marihuana provided by Health Canada is comprised of the mature flowering heads of female plants and contains $12.5 \pm 2\%$ total THC (Δ^9 -THC and Δ^9 -THC acid) and less than 0.5% CBD, CBG, CBN, CBC (7). The MS-17/338 production line has THC concentrations typically higher than 10%, with the mature flowering heads containing the highest concentration of THC (7). The plant is cultivated and harvested in compliance with Good Manufacturing Practices, by Prairie Plant Systems Inc. under contract to Health Canada (8). The product is irradiated to ensure that users whose immune systems may be compromised are not exposed to toxic spores which occur naturally in the plants (7).

1.2 Other ingredients

Marihuana smoke contains many of the same carcinogenic chemicals found in tobacco smoke (2,9,10). However, 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 smoking compared to tobacco smoking (11). This greater retention of tar and carbon monoxide from cannabis smoke may compensate for the fact that a marihuana smoker typically smokes fewer cigarettes per day than a tobacco smoker (i.e., the exposure to tar and carbon monoxide could be similar for both groups of smokers) (12,13). A systematic comparison of the mainstream smoke composition from marihuana (Health Canada product) and tobacco cigarettes prepared in the same way and consumed in an identical manner under two different sets of smoking conditions ("standard" and "extreme") has been reported (10). The "standard" condition reflects typical tobacco cigarette smoking conditions, whereas the "extreme" condition approaches that typically seen in marihuana smoking (10). Ammonia in mainstream marihuana smoke was 20-fold greater than that found in tobacco smoke and oxides of nitrogen and hydrogen cyanide were 3-5 times higher than those in tobacco smoke. Carbon monoxide was significantly lower in mainstream marihuana smoke, under both smoking conditions. Tar was statistically significantly higher in mainstream marihuana smoke only under the "extreme" smoking condition.

1.3 Stability and storage

Most of the information on the stability of marihuana does not distinguish between THC and its carboxylic acid (THCA). The latter is degraded to THC by pyrolysis during smoking or in the inlet of gas chromatographs used in forensic analysis (14). Heat, light, humidity, acidity and oxidation all affect the stability of cannabis (15,16). The National Institute on Drug Abuse (NIDA) reports that retention samples of their carefully prepared and standardized cigarettes are stable for months, particularly when stored below 0°C (-18 °C) in the dark in tightly-closed containers (17). Even when stored at +18°C, only a third of the THC content is lost over a 5-year period with some increase in the concentration of CBN. Lower-potency cigarettes (1.15%) appear to lose more THC compared to higher potency cigarettes (2.87%) (17).

2.0 Clinical Pharmacology

2.1 Pharmacodynamics

Two types of cannabinoid receptors, CB₁ and CB₂, have been identified each with distinct patterns of tissue expression. CB₁ receptors are most abundant in nervous tissue but are also found in adipocytes, leukocytes, spleen, heart, lung, liver, pancreas, kidney, reproductive organs, skeletal muscle and skin; CB₂ receptors are most highly concentrated in the tissues and cells of the immune system such as leukocytes and spleen but can also be found to a lesser degree in bone, liver and also in some neurons (reviewed in (18) and also in (19)). Most tissues contain a functional

endocannabinoid system which consists of the cannabinoid receptors (CB₁ or CB₂), the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and their “entourage” compounds which modulate endocannabinoid activity, and endocannabinoid synthesizing and degrading enzymes (20).

Much of the pharmacodynamic information on marijuana refers to the effects of the major constituent THC which has activity at both CB receptors but whose psychoactive effects are mediated by the CB₁ receptor (21). On the other hand, CBD lacks detectable psychoactivity but displays high potency as an antagonist of CB₁/CB₂ receptor agonists and affects the activity of a significant number of other targets including ion channels, receptors, and enzymes (reviewed in (22)). Results from pre-clinical studies suggest CBD has anti-inflammatory, analgesic, antipsychotic, anti-ischemic, anxiolytic, and antiepileptic effects (reviewed in (22)). CBN is a product of Δ^9 -THC oxidation and has 10% of the activity of Δ^9 -THC (22). Its effects are not well studied but it appears to have some immunosuppressive properties (23). CBG is a partial CB_{1/2} receptor agonist and may have some anti-inflammatory and analgesic properties (24,22). Much of what is known about the beneficial properties of these non-psychotropic cannabinoids was derived from *in vitro* and animal studies and few, if any, clinical studies of these substances exist. However, the results from these *in vitro* and animal studies point to potential therapeutic indications such as psychosis, epilepsy, anxiety, sleep disturbances, neurodegeneration, cerebral and myocardial ischemia, inflammation, pain and immune responses, emesis, food intake, type-1 diabetes, osteogenesis, and cancer (reviewed in (22)). For more in-depth information on the pharmacology of cannabinoids, the reader is invited to consult the following resources (25,22).

Table 1 (next page), adapted from the British Medical Association Report (2), notes some of the pharmacological effects of cannabis in the therapeutic dosage range. Many of the effects are biphasic, with increased activity with acute or smaller doses, and decreased activity with larger doses or chronic use (26,2). Effects differ greatly among individuals and may be greater in those who are severely ill, elderly, or those taking other drugs.

The acute effects of smoking marijuana include almost immediate euphoria (the marijuana “high”) as well as cardiovascular, bronchopulmonary, ocular, psychological and psychomotor effects. Maximum euphoria occurs within 15 minutes after smoking; the psychological effects reach a plateau which can last for several hours (6). However, on first dosing, some people experience dysphoria and anxiety (27). The effects on the cardiovascular system (tachycardia, etc.) decline much faster as THC is distributed out of the circulatory system. Tachycardia is the most consistent of the physiological effects of marijuana (28,29).

The short-term psychoactive effects of marijuana smoking include the above-mentioned euphoria as well as relaxation, time-distortion, intensification of ordinary sensory experiences (such as eating, watching films and listening to music) and loss of inhibitions that may result in laughter (30). This is followed by a depressant period (31). While there is some inconsistency in reports regarding the acute effects of cannabis on memory and motor skills (32,33,34), most reviews note that marijuana use is associated with impaired function on a variety of cognitive and short-term memory tasks (35,31,23,36). The levels of THC in the plasma after smoking appear to have a dose and concentration dependent effect on cognitive function (37). Driving and operation of intricate machinery, including aircraft, may be significantly impaired (38,39,40,41).

Table 1: Pharmacologic actions of cannabis in humans (2)

Body System/Effect	Detail of Effects
Central Nervous System (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 with other CNS depressants.
Cognition, psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance especially in complex and demanding tasks.
Motor function	Increased motor activity followed by inertia and incoordination, ataxia, dysarthria, tremulousness, weakness, muscle twitching.
Analgesic	Similar in potency to codeine but by a different pharmacological 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” (with chronic use).
Dependence, abstinence syndrome	Has been produced experimentally following prolonged intoxication: symptoms include disturbed sleep, decreased appetite, restlessness, irritability and sweating.
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 (with chronic use, but tolerance may develop).
Females	Suppression of ovulation, complex effects on prolactin secretion; increased obstetric risk with chronic use.

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[®]) and Sativex[®] (Δ^9 -THC and CBD) as well as other routes of administration.

2.2.1 Absorption

2.2.1.1 Smoked cannabis

The amount of Δ^9 -THC delivered from cannabis cigarettes is not uniform and is a major variable in the assessment of absorption (5). Uncontrolled factors include the source of the plant material and the composition of the cigarette, together with the efficiency and method of smoking used by the subject (42,5). Smokers often titrate their THC intake adapting their smoking behaviour to obtain desired levels of THC by taking more puffs and/or inhaling more efficiently depending on the strength of THC (43). THC absorption by inhalation is extremely rapid but quite variable, with a bioavailability of 2 to 56% through the smoking route depending on depth of inhalation, puff duration and breathhold (44,45). Standardised cigarettes have been developed by the National Institute on Drug Abuse (NIDA), and the relationships among cannabis THC content, dose administered and resultant plasma levels have been investigated. Smoking cannabis containing 1.64% THC (mean dose 13.0 mg THC) resulted in mean peak THC plasma levels of 77 ng/mL (46).

2.2.1.2 Vaporized cannabis

Vaporization of cannabis has been explored as an alternative to smoking. The advantages of vaporization apparently include the formation of a smaller quantity of toxic by-products such as carbon monoxide, polycyclic aromatic hydrocarbons (PAHs) and tar, as well as a more efficient extraction of THC from the cannabis material (47,48,49,43,50). The subjective effects and plasma concentrations of THC are comparable to those of smoked cannabis with absorption being somewhat faster with the vaporizer (43). The vaporizer is well-tolerated, with no reported adverse effects, and is generally preferred over smoking by most subjects (43). While vaporization is amenable to self-titration (49,43), the proper use of the vaporizer for optimal administration of medicinal cannabis has to be established in more detail (50). The amount and type of cannabis placed in the vaporizer, the vaporizing temperature and duration of vaporization, and the balloon volume are some of the parameters that can affect the delivery of THC (49). Bioequivalence of vaporization compared to smoking has not been established.

2.2.1.3 Oral THC

THC can be absorbed orally by ingestion of foods containing cannabis (butters, oils, brownies, cookies), teas prepared from leaves and flowering tops, or through ingestion of capsules containing THC or THC analogues. Absorption from an oral dose of 20 mg THC in a chocolate cookie was described as slow and unreliable (42), with a systemic availability of only 4 to 12% (46). While most subjects displayed peak plasma THC concentrations between 1 to 2 h, some of the 11 subjects in the study only peaked at 6 h and many had more than one peak. Consumption of cannabis-laced brownies containing 2.8% THC was associated with changes in behaviour although the effects were slow to appear and variable (51). Peak effects occurred 2.5 to 3.5 h after dosing. Modest changes in pulse and blood pressure were also noted. Tea made from dried cannabis flowering tops (19.1% THCA, 0.6% THC) has been documented, but the bioavailability of THC from such teas is likely to be smaller than that achieved by smoking (52). Only 10-20% of synthetic THC (dronabinol, Marinol[®]) administered in capsules with sesame oil enters the systemic circulation indicating extensive first-pass metabolism (53). The psychotropic effect or "high" occurs more quickly by the smoking than the oral route, which has been characterized by Iversen (54) as the reason "smoking is the preferred route of cannabis for many people".

2.2.1.4 Buccal THC

Following a single buccal administration of Sativex[®] (four sprays of Δ^9 -THC 27mg/mL and CBD 25 mg/mL, totalling 10.8mg Δ^9 -THC and 10 mg CBD), peak plasma concentrations of both THC and CBD typically occur within 2-4 h (55). When administered buccally, blood levels of THC and other cannabinoids are lower than those achieved by inhalation of the same dose of smoked cannabis because absorption is slower, redistribution into fatty tissue is rapid and some of the THC undergoes hepatic first-pass metabolism to 11-hydroxy-THC (55).

2.2.1.5 Rectal THC

Limited evidence suggests a higher bioavailability of THC by the rectal route than by the oral route due to higher absorption and decreased first-pass metabolism (56,57). In humans, rectal doses of 2.5-5.0 mg THC were associated with peak plasma levels of THC ranging from 1.1 to 4.1 ng/mL and 6.1 to 42.0 ng/mL hydroxy-THC within 2-8 h and 1-8 h (respectively) after administration (56). Data from animal studies indicate that in contrast to pure Δ^9 -THC, rectal administration of the hemisuccinate ester of Δ^9 -THC resulted in higher bioavailability of Δ^9 -THC (52-61%) (58,59,60). Plasma concentrations of Δ^9 -THC were dose and vehicle-dependent and also varied according to the chemical structure of the THC ester (59). In dogs, a dose of the hemisuccinate ester equivalent to 5 mg of Δ^9 -THC yielded a peak mean plasma concentration of 27 ng/mL Δ^9 -THC within an hour after administration; a 10 mg equivalent dose yielded a peak concentration of 118 ng/mL 2 h after dosing; a 20 mg dose gave a 190 ng/mL peak mean plasma concentration one hour after administration (59).

2.2.1.6. Topical THC

Cannabinoids are highly hydrophobic, making transport across the aqueous layer of the skin the rate-limiting step in the diffusion process (5). No clinical studies on the percutaneous absorption of cannabis-containing ointments, creams or lotions exist. However, some research has been carried out on transdermal delivery of synthetic and natural cannabinoids using a dermal patch (61,62). Mean steady-state plasma concentration of Δ^8 -THC was 4.4 ng/mL within 1.4 h, and was maintained for at least 48 h (61). Permeabilities of cannabidiol (CBD) and cannabinol (CBN) were found to be 10-fold higher than for Δ^8 -THC (63).

2.2.2 Distribution

Distribution of THC begins immediately after absorption where it is taken up primarily by fatty tissues and highly perfused organs such as the heart, lung, brain and liver (5). THC has a large apparent volume of distribution, approximately 10 L/kg, because of its high lipid solubility (64). The plasma protein binding of THC and its metabolites is approximately 97% (65,66). THC is mainly bound to low-density lipoproteins, with up to 10% present in red blood cells (67), while the metabolite, 11-hydroxy THC, is strongly bound to albumin with only 1% found in the free-fraction (68).

The highest concentrations of THC are found in the heart and in adipose tissue, with levels reaching 10 and 1000 times that of plasma, respectively (69). Despite the high perfusion level of the brain, the blood-brain barrier (BBB) appears to limit the access and accumulation of THC in this organ (70) and the slight delay in correlating peak plasma concentration to psychoactive effects may be attributed to the time required for THC to traverse this barrier (42).

THC accumulates and is retained in fatty tissue, and its release from this storage site into the blood is slow (70). It is not certain if THC persists in the brain in the long-term; however, the presence of acute cognitive deficits in abstinent heavy cannabis users raises the possibility that THC may be retained in the brain at least in the short term (71,72). One animal study suggested food deprivation or adrenocorticotrophic hormone (ACTH) administration in rats accelerates lipolysis and the release of THC from fat stores, however further research is needed to determine if these effects are associated with intoxication or behavioural/cognitive changes (73).

2.2.3 Metabolism

Most cannabinoid metabolism occurs in the liver and different metabolites predominate depending on the route of administration (42,5). The complex metabolism of THC involves allylic oxidation, epoxidation, decarboxylation and conjugation (42). THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19 and 3A4 (5). The major initial metabolites of THC are the active 11-hydroxy THC and the non-active 11-nor-9-carboxy THC (5). 11-hydroxy THC is rapidly formed by the action of hepatic microsomal oxidases, and plasma levels parallel the duration of observable drug action (74,75). 11-hydroxy THC has psychotomimetic properties equal to those of THC (76,77). The psycho-inactive 11-nor-9-carboxy THC is the primary acid metabolite of THC excreted in urine (78) and it is the cannabinoid often screened for in forensic analysis of body fluids (79,80).

Xenobiotics are not only metabolized by CYPs but they also modulate the expression level and activity of these enzymes; they are therefore a focal point in drug-drug interactions and adverse drug reactions (81). Polyaromatic hydrocarbons found in tobacco (and cannabis) smoke induce the expression of CYP1A2 (82) while THC, cannabidiol (CBD), and cannabinol (CBN) inhibit CYP1A1, 1A2 and 1B1 enzymes (83). CBD has also been shown to inhibit formation of THC metabolites catalyzed by CYP3A4, with less effect on CYP2C9 (64), albeit sufficiently to decrease the formation of 11-hydroxy THC (84).

While minimal information is available in the literature, results from some *in vitro* experiments indicate that THC also inhibits CYP3A4, CYP2C9 and CYP2C19, while CBD inhibits CYP2C19, although higher concentrations than those seen clinically are required for inhibition (55). Few studies have specifically evaluated cannabis-drug interactions. Therefore, although the clinical significance of potential metabolic interactions through these pathways has not been established, clinicians should carefully monitor patients who are concomitantly consuming cannabis and other medications that are metabolized by these enzymes. For example, the Sativex[®] product monograph cautions against combining Sativex[®] with amitriptyline or fentanyl (or related opioids) which are metabolized by CYP3A4 and 2C19 (55). Cannabis smoking as well as orally administered dronabinol may also affect the pharmacokinetics of antiretroviral medications (85). In addition, and as seen with tobacco smoke, cannabis smoke has the potential to induce CYP1A2, increasing the metabolism of xenobiotics biotransformed by this isozyme such as theophylline (86) or the antipsychotic medications clozapine or olanzapine (87). Further information on drug-drug interaction can be found in section 7.3.

2.2.3.1 Inhalation

Plasma values of 11-hydroxy THC appear rapidly and peak shortly after THC, at about 15 minutes after the start of smoking (88). Peak plasma concentrations are approximately 5%-10% of parent THC and the area under the curve (AUC) profile of this metabolite averages 10-20% of the parent THC (75). Similar results were obtained with intravenous THC administration (89).

Peak plasma values of 11-nor-9-carboxy THC occur 1.5 to 2.5 h after smoking and are about one third the concentration of parent THC (88). Following oxidation, the phase II metabolites of the free drug or hydroxy-THC appear to be glucuronide conjugates (42).

2.2.3.2 Oral

After oral doses of THC, parent THC and its active metabolite, 11-hydroxy-THC which is similar to or greater in potency than THC, are present in approximately equal concentrations in plasma (90,51). Concentrations of both parent drug and metabolite peak at approximately 2 to 4 h after oral dosing and decline over several days. Clearance averages about 0.2 L/kg-h, but is highly variable, due to the complexity of cannabinoid distribution (53). The plasma levels of active 11-hydroxy metabolite are about 3 times higher than observed in the plasma from smoking (75).

2.2.4 Excretion

THC levels in plasma decrease rapidly after cessation of smoking. Mean THC plasma concentrations are approximately 60% and 20% of peak concentrations 15 and 30 min post-smoking respectively (91) and are below 5 ng/mL 2 h after smoking (45). However, THC from a single dose can be detected in plasma for at least a day and up to 13 days in chronic smokers (92). The decline of THC in plasma is multiphasic and as Harvey (64) notes, the estimates of the terminal half-life of THC in humans have progressively increased as analytical methods have become more sensitive. While figures for the terminal elimination half-life of THC appear to vary, it is probably safe to say that it averages at least a week and could be considerably longer. Low levels of THC metabolites have been detected for more than 5 weeks in the urine and feces of cannabis users (64). The degree of THC use does not appear to influence the plasma half-life of THC (89).

Following inhalation (or intravenous administration), elimination of THC and its metabolites occurs via the feces (65%) and the urine (20%) (5). After five days, 80% to 90% of the total dose is excreted (75). Similarly, following oral doses, THC and its metabolites are excreted in both feces and urine (75). Biliary excretion is the major route of elimination with about half of a radiolabelled oral dose being recovered from the feces within 72 h in contrast to the 10 to 15% recovered from urine (75).

2.3 Pharmacokinetic-pharmacodynamic relationships

The temporal relationship between plasma concentrations of THC and the associated psychotropic, cognitive and motor effects is unclear (93,94). Furthermore, dose and plasma concentration versus response for possible therapeutic applications are ill-defined, except for some information obtained for oral dosing with dronabinol (synthetic THC) for its limited indications (53). Interpretations of the pharmacokinetics of THC are also complicated by the presence of active metabolites, particularly 11-hydroxy THC, which are found in higher concentrations after oral administration than after inhalation (90,51).

Target THC plasma concentrations have been derived based on the subjective “high” response that may or may not be related to the potential therapeutic applications. Various pharmacodynamic models provide steady-state blood plasma concentration estimates in the range of 7-29 ng/mL THC necessary for the production of a 50% maximal subjective “high” effect (93). Serum concentrations between 7 and 10 ng/mL (whole blood, approximately 3-5 ng/mL) have been compared to a blood-alcohol concentration of 0.05% which is associated with driver impairment (95). Simulation of multiple dosing with a 1% THC cigarette containing 9 mg THC yielded a maximal “high” at about 45 minutes after dosing, declining to 50% of peak at about 100 minutes following smoking (94). A dosing interval of 1 h with this dose would give a “continuous high” and the recovery after the last dose would be 150 minutes. The peak THC plasma concentration during this dosage is estimated at about 70 ng/mL and the steady-state THC plasma concentration at 50% of the maximum “high” effect ($C_{ss}(50)$) at about 30 ng/mL THC.

3.0 Dosing

Precise dosages for cannabis have not been established. The complex pharmacology of cannabinoids, interindividual differences in cannabinoid bioavailability, prior exposure to and experience with cannabis, the variable potency of the plant material, and different dosing regimens used in different research studies all contribute to the difficulty in reporting precise doses or establishing uniform dosing schedules (91,96). Nevertheless, some “rough” dosing guidelines for smoked or vaporized marijuana have been published (see below). Besides smoking and vaporization, marijuana is known to be consumed in baked goods such as cookies or brownies or drunk as teas or infusions. However, absorption by the oral route is slow and erratic (see section 2.2) and dosages are even less well established in these cases (51,97,98,52). Other forms of preparation reported in the lay literature include cannabis-based butters, oils, compresses, creams, ointments, and tinctures (99,6,100,101,102) but again, little or no dosing information exists here and much of the information is anecdotal in nature. Patients with no prior experience with marijuana and initiating marijuana therapy for the first time are cautioned to begin at a very low dose and to stop therapy if unacceptable or undesirable side effects occur.

3.1 Smoking

According to the World Health Organization (WHO) (103), a typical joint contains between 0.5 and 1.0 g of cannabis plant matter (average 750 mg) which may vary in THC content between 7.5 and 225 mg (i.e. typically between 1 and 30%; see Table 2). The amount of other cannabinoids present, mainly cannabinol (CBN) and cannabidiol (CBD), is usually much lower. The actual amount of THC delivered in the smoke varies widely and has been estimated at 20 to 70%, the remainder being lost through combustion or side-stream smoke (96). Furthermore, the bioavailability of THC (the fraction of THC in the cigarette which reaches the bloodstream) from the smoking route is variable (2-56%) and influenced by the smoking topography (the number, duration, and spacing of puffs, hold time and inhalation volume) (45). In addition, expectation of drug reward can also influence smoking dynamics (104). Thus, the actual dose of THC absorbed when smoked is not easily quantified.

Table 2: Relationship between THC percent in plant material and the available dose in an average joint.

% THC (mg per 100 mg cannabis)	mg THC per 750 mg * (“average joint”)
1	7.5
2.5	18.75
5	37.5
10	75
15	112.5
20	150
30	225

* WHO average weight

Using a paced smoking protocol, the mean plasma concentration of THC after a first inhalation of a marijuana cigarette containing 3.55% THC has been reported to be 18.1 ng/mL (1.8-37.0 ng/mL) with the mean peak plasma concentration reaching 162 ng/mL (76-267 ng/mL) after 7 puffs or almost complete smoking of the cigarette (91,45). Peak plasma concentrations of THC in the range of 50-100 ng/mL associated with a subjective “high” (section 2.3) can thus be easily attained by smoking a single 3.55% THC marijuana cigarette (900 mg plant material, 32 mg THC) (91). A 750 mg joint of 5% strength (i.e., 37.5 mg THC) would yield slightly higher plasma levels. If the current average “street” marijuana contains 10% THC, then plants yielding joints from such a source might have an available 75 mg dose and could result in rapid attainment of plasma THC concentrations above 300 ng/mL. The availability of even more potent strains of marijuana would yield even higher plasma concentrations of THC.

There are few, if any, efficacy studies on the amounts of cannabis required for a therapeutic effect. However, one recent Canadian study showed that a single inhalation of a 25 mg dose of smoked marijuana (THC content 9.4%) yielded a mean plasma THC concentration of 45 ng/mL within 2 minutes after initiating smoking (105). Various surveys have reported that people using smoked cannabis for medical purposes used between 10-20 grams of cannabis per week or approximately 1-3 grams per day (96,106,107). Assuming cannabis with 15% THC, this would suggest an intake between 34-68 mg of THC per day (96).

3.2 Oral

The pharmacokinetic information described in section 2.2 reports the erratic and slow absorption of THC from the oral route and oral doses are estimated from the information for Marinol[®]. A 10 mg b.i.d. dose of Marinol[®] (20 mg total per day) yielded a mean peak plasma THC concentration of 7.88 ng/mL (53). By comparison, consumption of a chocolate cookie containing 20 mg THC resulted in peak plasma THC concentrations ranging from 4.4 to 11 ng/mL, with a bioavailability of 6% (46). Tea prepared from *Cannabis* flowering tops and leaves has been documented but no data is available regarding efficacy (52).

3.3 Buccal

Dosing with Sativex[®] is described in the product monograph along with a titration method for proper treatment initiation (55).

3.4 Vaporization

The Dutch Office of Medicinal Cannabis has published “rough” guidelines on the use of vaporizers (52). Although the amount of cannabis used per day needs to be determined on an individual basis, the initial dosage should be low and may be increased slowly as symptoms indicate. The amount of cannabis to be placed in the vaporizer may vary depending on the type of vaporizer used. Studies using the Volcano[®] vaporizer have reported using up to 1 gram of dried cannabis in the chamber but 50 to 500 mg of plant material is typically used (50); THC concentrations up to 6.8% have been tested (43,50). Subjects appeared to self-titrate their intake in accordance with the THC content of the cannabis (43). The levels of cannabinoids released into the vapour phase increased with the temperature of vaporization (50). Vaporization temperature is typically between 180-195°C (52); higher temperatures (230°C) greatly increase the amounts of cannabinoids released but also increase the amounts of by-products (50).

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 the treatment of severe nausea and vomiting associated with cancer chemotherapy and for AIDS- related anorexia associated with weight loss (53).

Sativex[®], a buccal spray containing Δ^9 -THC 27 mg/mL and CBD 25 mg/mL is marketed (with conditions) in Canada as an adjunctive treatment for the symptomatic relief of neuropathic pain in adults with multiple sclerosis and as an adjunctive analgesic in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (55).

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 generally inconclusive. The existing scientific evidence for cannabinoids in treating various symptoms is summarized in the following sections.

4.1 Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing and common adverse events associated with cancer treatment (108). Patient claims that smoked cannabis relieves CINV are widely recognized. Cannabinoid CB₁ and CB₂ receptors have been found in areas of the brainstem associated with emetogenic control (109,110) and results from animal studies suggest the anti-emetic properties of cannabinoids are most likely related to their agonistic actions at CB₁ receptors (111,112). However, an *in vitro* study has shown that THC also antagonizes the 5-HT₃ receptor (113) raising the possibility that cannabinoids may exert their anti-emetic action through more than one mechanism. The evidence for cannabinoids such as nabilone (Cesamet[®]), dronabinol and levonantradol in treating CINV has been reviewed (114,115). While cannabinoids present clear advantages over placebo in the control of CINV, the evidence from randomized trials shows cannabinoids to be clinically only slightly better than conventional dopamine D2-receptor antagonist anti-emetics (114,115). In some cases, patients appeared to prefer the cannabinoids over these conventional therapies despite the increased incidence of adverse effects such as drowsiness, dizziness, dysphoria, depression, hallucinations, paranoia, and arterial hypotension. For certain patients, a degree of sedation and euphoria may be perceived as beneficial during chemotherapy. No clinical trials directly comparing cannabinoids to newer anti-emetics such as 5-HT₃ (Ondansetron, Granisetron) or NK-1 receptor antagonists have been reported to date (115,108). The use of cannabinoids (whether administered orally or by smoking) is currently considered a fourth-line adjunctive therapy in CINV when conventional anti-emetic therapies have failed (116,117,118,119,120,121). Few studies on the effects of combining cannabinoids and 5-HT₃ antagonists to treat

CINV exist. In one clinical study with a small sample size, the combination of dronabinol and ondansetron did not provide added benefit beyond that observed with either agent alone (122). However, an animal study showed that low doses of THC when combined with low doses of the 5-HT₃ receptor antagonist tropisetron were more efficacious in reducing emesis frequency than when administered individually (123). More research is required to determine if combination therapy provides added benefits above those observed with newer standard treatments.

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

4.2.1 To stimulate appetite and produce weight gain in AIDS patients

The ability of cannabis to increase appetite has been recognized anecdotally for many years (124). Results from epidemiological studies suggest that people actively using marijuana have higher intakes of energy and nutrients than non-users (125). Controlled laboratory studies with healthy subjects suggest exposure to marijuana whether by inhalation or oral ingestion of THC-containing capsules, correlates positively with an increase in food consumption, caloric intake and body weight (126,124). Studies showing a high concentration of CB₁ receptors in brain areas associated with control of food intake and satiety lend further support to the link between cannabis consumption and appetite regulation (127,128,129). Increasing evidence also suggests a role for the endocannabinoid system in modulating appetite, food intake and energy metabolism (reviewed in (128,129)).

The ability of marijuana to stimulate appetite and food intake has been applied to clinical situations where weight gain is deemed beneficial such as in HIV-associated muscle wasting and weight loss. One study showed that experienced HIV+ marijuana smokers with clinically significant muscle mass loss benefited from both dronabinol (4-8 times the standard 2.5 mg b.i.d dose or 10-20 mg daily) and smoked marijuana (3 puffs at 40 sec intervals, 1.3-3.9% THC). Both drugs produced substantial and comparable increases in food intake and body weight, as well as improvements in mood and sleep (130,131). The marijuana-associated increase in body weight appeared to result from an increase in body fat rather than lean muscle mass (132,133).

Oral synthetic THC, dronabinol, administered as capsules (Marinol[®]) is an approved indication in Canada for AIDS-related anorexia associated with weight loss. The Marinol[®] product monograph summarizes a randomized double-blind, placebo controlled-trial in 139 patients with the 72 patients in the treatment group initially receiving 2.5 mg dronabinol twice a day, then reducing the dose to 2.5 mg at bedtime due to side effects (feeling high, dizziness, confusion and somnolence) (134). Over the six week treatment period dronabinol significantly increased appetite, with a trend towards improved body-weight, and mood, and a decrease in nausea. At the end of the six week period, patients were allowed to continue receiving dronabinol, during which appetite continued to improve (135). This open-label, 12 month follow-up study suggested that dronabinol was safe and effective for long-term use for the treatment of anorexia associated with weight loss in patients with AIDS (135).

4.2.2 To stimulate appetite and produce weight gain in cancer patients

Anorexia is ranked as one of the more troublesome symptoms associated with cancer, with more than half of patients with advanced cancer experiencing a lack of appetite and/or weight loss (136,137). While it is anecdotally known that smoking marijuana can stimulate appetite, the effects of smoking marijuana on appetite and weight gain in patients with cancer cachexia have not been studied. The results from trials with oral THC (dronabinol) or oral cannabis extract are mixed and the effects, if any, appear to be modest. In two early studies, oral THC (dronabinol) improved appetite and food intake in some patients undergoing cancer chemotherapy (138,139). An open-label study of dronabinol (2.5 mg, 2-3 times daily, 4-6 weeks) in patients with unresectable or advanced cancer reported increases in appetite and food intake, but weight gain was only achieved in a few patients (140,141,142). Modest weight gain was obtained with a larger dose regimen of dronabinol (5 mg, 3 times daily), but the central nervous system side effects including dizziness and somnolence were limiting factors (143). In contrast, a randomized, double-blind placebo-controlled study involving cancer patients with related anorexia-cachexia syndrome failed to demonstrate any differences in patients' appetite across treatment categories (oral cannabis extract, THC or placebo) (144). Furthermore, when compared to megestrol acetate, an orexigenic medication, dronabinol was significantly ($p < 0.001$) less efficacious in reported appetite improvement and weight gain (145). According to a recent review of the medical management of cancer cachexia, the current level of evidence for cannabinoids such as dronabinol in the treatment of this condition is low (146). Cancer cachexia is not an approved indication for dronabinol either in Canada or the U.S.

4.2.3 Anorexia nervosa

The endocannabinoid system has been implicated in appetite regulation and is suspected to play a role in eating disorders such as anorexia nervosa (147,128). However, genetic studies have failed to agree on an association between genes coding for endocannabinoid system proteins and anorexia nervosa in spite of epidemiological and familial studies which suggest a genetic basis for this disorder (148,149). Little information exists on the use of marihuana to treat anorexia nervosa. No studies have looked at the effects of smoking marihuana and a randomized trial of oral THC failed to demonstrate weight gain in anorexic patients (150). Furthermore, three of the eleven patients administered THC also reported severe dysphoric reactions. Both the British Medical Association (2) and the Institute of Medicine (116) concluded that marihuana was unlikely to be effective in this group of patients.

4.3 Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury

Anecdotal reports suggest marihuana can ameliorate spasticity in patients suffering from multiple sclerosis (MS) or spinal cord injury when other drugs fail or produce unacceptable side effects (2,151,116).

4.3.1 Multiple sclerosis

In humans, published reports spanning one hundred years suggest that people with spasticity may experience relief with cannabis (152). In the UK, 43% of patients with MS reported having experimented with cannabis at some point and 68% of this population used it to alleviate the symptoms of MS (153). In Canada, the prevalence of medicinal use of cannabis among patients seeking treatment for MS in 2000 was reported to be 16% in Alberta, with 43% stating they had used cannabis at some point in their lives (154). Fourteen percent of people with MS surveyed in 2002 in Nova Scotia reported using cannabis for medical purposes, with 36% ever having used cannabis for any purpose (106). MS patients reported using cannabis to manage symptoms such as spasticity and chronic pain as well as anxiety and/or depression (154,106). Patients also reported improvements in sleep. Reputed dosages of smoked cannabis by these patients varied from a few puffs to 1 gram or more at a time (106).

The results of randomized, placebo controlled trials with cannabinoids for the treatment of muscle spasticity are encouraging but modest. The large multicentre randomized placebo-controlled CAMS (Cannabis in Multiple Sclerosis) study researching the effect of cannabinoids for the treatment of spasticity and other symptoms related to MS enrolled over 600 patients (155). The primary outcome was change in overall spasticity scores using the Ashworth scale. The study did not show any statistically significant improvement in the Ashworth score in patients on oral cannabis extract or oral THC. However, there was evidence of a treatment effect on patient-reported spasticity and pain ($p=0.003$), with improvement in spasticity using either cannabis extract (61%) or THC (60%) compared to placebo (46%). Other randomized clinical trials on Sativex[®] (156,157) and standardized cannabis extract capsules (158) reported similar results, in that improvements were only seen in patient reports but not with objective measures. Spasticity is a complex phenomenon (159), is inherently difficult to measure and has no single defining feature (157). Furthermore, the reliability and sensitivity of the Ashworth scale has been called into question (155,157). Nevertheless, a long-term (12 months) follow-up to the CAMS study showed evidence of a small treatment effect of oral THC on muscle spasticity measured by objective methods (160). However, the clinical significance of this change from the patient perspective remained uncertain. A long-term, open-label, follow-up study of Sativex[®] concluded that the beneficial effect was maintained in patients who had initially benefited from the drug (161). In summary, although the subjective experience of symptom reduction was generally found to be significant, objective measures of spasticity did not reach statistical significance in the majority of clinical studies.

Generally speaking, orally administered cannabinoids are well tolerated (162,158,163). Clinical trials to date do not indicate serious adverse effects associated with the use of cannabis-based medicinal extracts to treat MS-related symptoms. However, information is lacking regarding the long-term adverse effects of cannabinoid use. The most commonly reported physical adverse effects are dizziness, drowsiness and dry mouth (155,163). A more recent study concluded that Sativex[®] treatment in cannabis-naïve MS patients was not associated with cognitive impairment (163). However, the study did raise the possibility that higher dosages could precipitate changes in psychological disposition, especially in those patients with a prior history of psychosis.

4.3.2 Amyotrophic lateral sclerosis

The endocannabinoid system has been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS) and under certain conditions, cannabinoids have been reported to delay disease progression and prolong survival in mouse models of ALS (reviewed in (164)). Anecdotal reports suggest decreased muscle cramps and fasciculations in ALS patients who smoke herbal cannabis or drink cannabis tea with up to 10% of these patients using cannabis for symptom control (165). Few clinical trials of cannabis for the treatment of symptoms associated with ALS exist and the results of the studies are mixed. In one 4-week, randomized, double-blind, cross-over pilot study of 19 ALS patients, 2.5-10 mg per day of dronabinol were associated with improvements in sleep and appetite but not cramps or fasciculations (166). In contrast, a shorter (2-week) study reported no improvement in these measures in ALS patients taking 10 mg per day of dronabinol (165). In either case, dronabinol was well tolerated with few side effects.

4.3.3 Spinal cord injury

Limited information exists regarding the use of cannabinoids to treat symptoms associated with spinal cord injury (SCI) such as pain, spasticity, muscle spasms, urinary incontinence and difficulties sleeping. No clinical trials of smoked marijuana for the treatment of these symptoms have been documented, but subjective improvements have been reported by patients smoking marijuana (167,116). Double-blind, cross-over, placebo-controlled studies of oral THC and/or THC:CBD extract (Sativex[®]) suggested modest improvements in pain, spasticity, muscle spasms and sleep quality in patients with SCI (168,116,169). A randomized, double-blind, placebo-controlled parallel study using a minimum of 15-20 mg THC/day (mean daily doses of 31 mg THC orally or 43 mg THC-hemisuccinate rectally) showed a statistically significant improvement in spasticity scores in patients with SCI (170). A more recent double-blind, placebo-controlled, cross-over study using nabilone (0.5 mg b.i.d.) also showed an improvement in spasticity compared to placebo in patients with SCI (171).

4.4 Epilepsy

In vitro studies as well as those carried out in animals generally suggest an anti-convulsant role for cannabinoids (172,173,174,175) however a pro-convulsant role has also been described (176). CB₁ receptors are located mainly presynaptically where they typically inhibit the release of classical neurotransmitters (177). The purported anti-epileptic effect of cannabinoids is thought to be mediated by CB₁-receptor dependent presynaptic inhibition of glutamate release (178); epileptogenic effects may be triggered by presynaptic inhibition of GABA release (179,172,173,180,175). CB₁ receptor agonists therefore have the potential to trigger or suppress epileptiform activity depending upon which cannabinoid-sensitive presynaptic terminals are preferentially affected (i.e. glutamatergic or GABAergic) (178).

Increasing evidence points to a role for the endocannabinoid system in the modulation of neuronal tone and excitability. Human and animal studies suggest epileptic activity is associated with changes in the levels and distribution of CB₁ receptors in the hippocampus (181,182,183) and reduced levels of the endocannabinoid anandamide have been detected in the cerebrospinal fluid of patients with untreated newly diagnosed temporal lobe epilepsy (184). These and other studies suggest dysregulation of the endocannabinoid system may play a role in epileptogenesis and could represent a target for anti-epileptic therapies. However, a review of the literature describing the effects of marijuana on epileptic symptoms in humans concluded that although cannabis use can reduce seizure frequency in some cases and provoke seizures in others, in the majority of cases it probably has no effect (185). This may be caused by the rather unspecific actions of exogenously administered cannabinoids such as THC which would target both excitatory and inhibitory neurons. Cannabidiol (CBD) has also been examined as a potential anti-epileptic in humans (see (186) for full review) but these early studies have not been followed up with larger and more convincing clinical trials.

4.5 Pain

4.5.1 Cancer pain

There are few properly controlled clinical trials of smoked marijuana for the treatment of cancer pain. Two randomized, double-blind, placebo-controlled studies suggested oral THC (dronabinol, Marinol[®]) provided an analgesic effect in patients suffering from moderate to severe continuous pain due to advanced cancer. The first (187) 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 and mental clouding was common. A second, placebo-controlled study (188) compared 10 and 20 mg oral

THC with 60 and 120 mg codeine in 36 patients with cancer pain. While the lower and higher doses of THC were equianalgesic to the lower and higher doses of codeine respectively, statistically significant differences in analgesia were only obtained between placebo and 20 mg THC and between placebo and 120 mg codeine. The 10 mg THC dose was well tolerated and, despite its sedative effect, appeared to have mild analgesic potential. The 20 mg THC dose induced somnolence, dizziness, ataxia, and blurred vision. Extreme anxiety was also observed at this dose in a number of patients. This side effect profile is supported by a report concerning a synthetic analogue of THC also tested in controlled trials (189). While it was equivalent in efficacy to codeine, it was not considered clinically useful because of the frequency of side effects. A recent randomized, double-blind, placebo-controlled, parallel-group trial of patients suffering from intractable cancer-related pain suggested that an orally administered THC:CBD extract containing 2.7 mg of THC and 2.5 mg CBD per dose (Sativex[®]) is an efficacious adjunctive treatment for pain not fully relieved by strong opioids (190). 43% of patients taking the extract achieved a 30% or greater improvement in their pain score which was twice the number of patients who achieved this response in the THC and placebo groups. Both the THC:CBD and the THC medications were well tolerated and adverse events were similar to those seen in other THC:CBD clinical trials (somnolence, dizziness, and nausea).

In Canada, Sativex[®] is approved (with conditions) as an adjunctive analgesic in cancer pain (55). It is indicated as an adjunctive analgesic treatment in adults with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent pain.

4.5.2 Non-cancer pain

Chronic, non-cancer pain is a complex syndrome that involves physical, psychological and psychosocial factors that contribute to a reduced quality of life (191). The anti-nociceptive efficacy of cannabinoids has been unequivocally demonstrated in several animal models of inflammatory and neuropathic pain (reviewed in (192)). Furthermore, animal studies have shown that cannabinergic modulation of neuronal circuits in the brain and spinal cord can inhibit nociceptive processing (193,194,195,196). More recent studies suggest that peripheral nociceptors also play a very important role in the modulation of cannabinoid-mediated analgesia (197). Less clear are the analgesic effects of smoked cannabis in experimentally-induced pain studies in human volunteers which have been inconclusive because of poor study design and conflicting results. Some studies on smoked cannabis report an analgesic effect (198,199) while a study on smoked cannabis (200) and one on oral cannabis (201) did not observe any analgesic effect. An experimental pain model applied to normal volunteers reports that oral THC and morphine provided synergistic analgesic effects (202). However, the authors caution that translating the results gathered from pain models and applying them in the clinic is not likely to be a straight forward process and that future studies should focus on clinical rather than experimental pain (202).

An off-label retrospective descriptive study of 20 adult patients suffering from chronic non-cancer pain of various etiologies reported subjective overall improvement and reduced pain intensity with nabilone as an adjunctive pain-relief therapy (191). Furthermore, beneficial effects on sleep and nausea were the main reasons for continuing use. A meta-analysis of all cannabinoid trials for analgesia concluded that as well as having effects on the CNS that limit their use, cannabinoids are no more effective than codeine as analgesics (203)

4.5.2.1 Postoperative pain

To date, there are only four published reports on the use of cannabis in postoperative pain (204,205,206,207). The conclusions from these studies were that cannabinoids are not ideally suited to manage postoperative pain, being either moderately effective (204,207), not different from placebo (205), or even antianalgesic at high doses (206). However, a definitive conclusion on the role of cannabinoids in the postoperative setting cannot yet be made because of the different drugs, dosages, routes of administration and protocols that were used in these studies (208).

4.5.2.2 Neuropathic pain

Cannabinoids suppress hyperalgesia and allodynia induced by diverse neuropathic states through CB₁ and CB₂-specific mechanisms (209). Short-term clinical studies suggest cannabinoids are moderately effective in reducing intractable central or peripheral neuropathic pain of various etiologies in individuals already receiving analgesic drugs (210). Side effects appear to be comparable to existing treatments and include dizziness, ataxia, a feeling of intoxication, xerostomia, dysgeusia, sedation and hunger (211). These effects may be minimized by employing low doses that are gradually escalated. The Canadian Pain Society considers cannabis-based therapies (dronabinol and Sativex[®]) to be fourth-line treatments for neuropathic pain, mostly as

adjuvant analgesics for pain conditions refractory to standard drugs (212). Health Canada has approved Sativex[®] (with conditions) as an adjunct treatment for the symptomatic relief of neuropathic pain in multiple sclerosis (MS) (55).

In one randomized controlled trial (RCT) using smoked cannabis, significant decreases in central and peripheral neuropathic pain that generally followed a linear dose-response relationship were reported (213). In another study, a greater than 30% decrease in HIV-associated sensory neuropathic pain was reported in 52% of patients smoking cannabis (3 times daily) compared to 24% in the placebo group (214). The number needed to treat (NNT) for 30% reduction in pain was 3.6 and was comparable to that reported for other analgesics in the treatment of chronic neuropathic pain. Yet another study showed a 30% decrease in HIV-associated distal sensory predominant polyneuropathic pain in 46% of patients smoking cannabis (1-8% Δ^9 -THC, four times daily) compared to 18% in the placebo group (215). The NNT in this study was 3.5. Cognitive changes appeared to be more pronounced with higher doses of Δ^9 -THC (213). More recently, an RCT of smoked cannabis for neuropathic pain caused by trauma or surgery and refractory to conventional therapies showed that compared to placebo, smoking 25 mg of cannabis containing 9.4% THC three times per day was associated with a modest but statistically significant decrease in average daily pain intensity (105). In addition, there were statistically significant improvements in measures of sleep quality and anxiety.

An RCT of patients suffering from MS-associated central neuropathic pain reported a decrease in central pain with daily doses of dronabinol (10 mg) (216). The number needed to treat for 50% pain reduction was 3.5. 54% of patients had a $\geq 33\%$ reduction in pain during dronabinol treatment compared with 21% of patients during placebo. The pain reduction in this study was comparable to that seen with other drugs commonly used in the treatment of neuropathic pain conditions (216).

A number of randomized, placebo-controlled, double-blind crossover and parallel studies have shown a significant reduction in central or peripheral neuropathic pain of various etiologies following treatment with Sativex[®] (217,218,219). In all three studies, patients were concomitantly using other analgesic drugs. The NNT for 30% pain reduction (deemed clinically significant) varied between 8 and 9 whereas the NNT for 50% pain reduction for central neuropathic pain was 3.7 and peripheral pain was 8.5.

While cannabidiol (CBD) was found to be an effective oral analgesic when administered chronically in a rat pain model (220), a study of oral CBD in 10 patients with chronic neuropathic pain found no significant pain relief (221).

4.5.2.3 Rheumatoid arthritis

A functional endocannabinoid system has been identified in the knee synovia of patients with end-stage osteoarthritis and rheumatoid arthritis (RA) (222). Furthermore, the levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) in the synovial fluid of patients with arthritis were increased compared to non-inflamed normal controls, although the significance of these findings is unclear (222). A preliminary study assessing the effectiveness of Sativex[®] in pain caused by rheumatoid arthritis, (223) reported a modest but statistically significant analgesic effect on movement and at rest, as well as on quality of sleep. Administration of Sativex[®] was well tolerated and no significant toxicity was observed. The mean daily dose in the final treatment week was 5.4 pump actuations (equivalent to 14.6 mg THC and 13.5 mg CBD) (223). Although the differences observed were small and variable across the participants, the results indicated a therapeutic potential for cannabinoids in RA and further research was suggested.

4.5.2.4 Headache

Historical and anecdotal evidence suggests a role for cannabinoids in the treatment of headache (224). Endocannabinoid deficiency has been postulated to underlie the pathophysiology of migraine (225). The concentrations of AEA are decreased in the cerebrospinal fluid of migraineurs, while the levels of calcitonin-gene-related-peptide (CGRP) and nitrous oxide (NO), normally inhibited by AEA and implicated in triggering migraine, are increased (226,227). In addition, the activity of AEA-degrading enzymes is significantly decreased in chronic migraineurs compared to controls (228). This drop in activity could represent a compensatory mechanism meant to elevate the low levels of AEA in migraine sufferers. Few, if any, clinical studies of cannabinoids to treat headache

exist. In one case report, a patient suffering from pseudotumour cerebri and chronic headache reported significant pain relief after smoking marihuana (229). In another case report, a patient complaining of cluster headaches refractory to multiple acute and preventive medications also reported dramatic improvement from smoking marihuana or taking dronabinol (5 mg) (230). These single-patient case-studies should be interpreted with caution and it should also be noted that marihuana use has been associated with reversible cerebral vasoconstriction syndrome and severe headache (231). In addition, headache is one of the most frequently reported physical symptoms associated with cannabis withdrawal (232). It is therefore possible that using marihuana simply relieves headache caused by marihuana withdrawal.

4.5.2.5 Fibromyalgia

A randomized, double-blind, placebo-controlled trial of nabilone 1 mg b.i.d. for the treatment of fibromyalgia showed statistically significant improvements in a subjective measure of pain relief and anxiety as well as on scores on the fibromyalgia impact questionnaire after 4 weeks of treatment (233). However, no significant changes in the number of tender points or tender point pain threshold were observed. Nabilone did not have any lasting benefit in subjects when treatment was discontinued.

4.6 Other diseases and symptoms

4.6.1 Movement disorders

The individual components of the endocannabinoid system (ligands, receptors, synthesizing and degrading enzymes) are particularly abundant in areas of the brain which control movement, such as the basal ganglia (234). Motor effects generally arise as a consequence of changes in endocannabinoid system activity with activation of the CB₁ receptor typically resulting in inhibition of movement (234). A number of studies have reported changes in CB₁ receptor levels and CB₁ receptor activity in motor diseases such as Parkinson's and Huntington's disease (235,236,237,238) and suggest a role for the endocannabinoid system in the pathology of these and other neurological diseases.

4.6.1.1 Dystonia

Anecdotal reports suggest cannabis might alleviate symptoms associated with dystonia (239); however no controlled studies of smoked marihuana in dystonic patients have been published. A six-week, open-label, pilot trial of five patients taking 100-600 mg/day of cannabidiol (CBD) reported modest dose-related improvements in all subjects but a worsening of tremor and hypokinesia in 2 patients with co-existing Parkinson's disease (240). Results of a double-blind, randomized, placebo-controlled study of 15 patients taking a single 0.03 mg/kg dose of nabilone showed no significant reduction in dystonia (241).

4.6.1.2 Huntington's disease

The relationship between the endocannabinoid system and Huntington's disease (HD) has been reviewed (242). Results from studies in animal models of HD as well as post-mortem studies in HD patients indicate downregulation and desensitization of CB₁ receptors in the brain (243,235,244,245,246,247). These findings suggest hypofunctionality of the endocannabinoid system may contribute to the pathophysiology of HD. This, together with the well-known protective properties of cannabinoid-related compounds, suggests that cannabinoids might help delay or arrest the development of the disease (242). However, there is little clinical evidence to support a role for cannabinoids in the treatment of HD, mostly because so few clinical trials have been carried out. In one double-blind, placebo-controlled, 15-week, cross-over trial of 15 patients with HD (248), 10 mg/kg/day of oral CBD did not improve the symptoms associated with HD. One randomized, double-blind, placebo-controlled, cross-over pilot study found little or no beneficial effect of nabilone over placebo in patients with HD (249). However, nabilone was well-tolerated and did not appear to exacerbate chorea or HD-associated psychosis, although some adverse effects such as drowsiness and forgetfulness were noted. The results from single-patient case studies are mixed. In one study, 1.5 mg nabilone increased choreatic movements (250), while in another case improved mood and decreased chorea was noted in a patient who had smoked cannabis and then continued on 1 mg nabilone b.i.d. (251).

4.6.1.3 Parkinson's disease

The role of cannabinoids in Parkinson's disease (PD) is complex. Endocannabinoid ligands, their synthesizing and degrading enzymes, and cannabinoid-activated receptors are highly abundant in the basal ganglia, the brain structures primarily affected in PD (234). While the levels of CB₁ receptors appear to be downregulated during the early, presymptomatic stages in a number of animal models of PD, increased CB₁ receptor density and function and elevated endocannabinoid levels are observed during the intermediate and advanced phases of the disease (237,252,253). These changes along with other factors such as the complex distribution of cannabinoid receptors within the basal ganglia may explain the paradoxical effects of cannabinoids in PD. Results from animal studies suggest cannabinoid receptor agonists induce hypokinesia and thus are unlikely to be a suitable first-line treatment for PD (254,234). On the other hand, cannabinoid-induced hypokinesia could be useful in attenuating the dyskinesia observed in PD patients on long-term levodopa treatment (254). Consistent with the complex pharmacology of cannabinoid receptors in the basal ganglia, the results of clinical trials examining the role of cannabinoids in the treatment of PD are mixed. One study involving five patients suffering from idiopathic PD found no improvement in tremor after smoking marijuana (1 g cigarettes containing 2.9% THC), whereas all subjects benefited from the administration of levodopa and apomorphine (255). A small randomized clinical trial of the synthetic cannabinoid nabilone in seven patients with PD found that the treatment reduced levodopa-induced dyskinesia (256). In contrast, a randomized double-blind crossover study demonstrated that oral cannabis extract did not produce any pro- or anti-parkinsonian action (257). Given the current state of knowledge, the benefits of using cannabinoids in the treatment of PD remain unestablished and further research is required.

4.6.1.4 Tourette's syndrome

Anecdotal reports have suggested amelioration of symptoms associated with Tourette's syndrome (TS) when smoking marijuana (258,259). A randomized, double-blind, placebo-controlled crossover trial of single oral doses of THC (5, 7.5 or 10 mg) in 12 adult patients with TS showed plasma concentration-related improvements in control of motor and vocal tics and obsessive-compulsive behaviour, with no serious side-effects; although transient, mild side-effects (headache, nausea, ataxia, fatigue, anxiety) were noted in five patients (260). In contrast to healthy marijuana users, neither a 5 mg nor a 10 mg dose of THC caused cognitive impairment (260). This study was followed up by a 6-week randomized, double-blind, placebo-controlled follow-up trial by the same group; they reported a significant difference in tic reduction compared to placebo in some patients and no detrimental effects on neuropsychological performance during or after treatment with 10 mg doses of THC (261). The major limitations of all three clinical studies were their small sample size and their relatively short duration. Therefore, although the results suggest THC benefits some patients suffering from TS, there is currently not enough evidence to fully support the use of cannabinoids in treating tics and obsessive-compulsive behaviour in people with TS (249).

4.6.2 Glaucoma

Glaucoma is a multifactorial disease characterized by the progressive degeneration of the optic nerve and the death of retinal ganglion cells (RGC) ultimately leading to irreversible blindness (262). Increased intraocular pressure (IOP) has been implicated in the pathophysiology of glaucoma, however inadequate blood supply to the optic nerve, oxidative damage, and apoptosis of RGCs are also contributing factors (263,264,262,265). Smoking or eating cannabis has been shown to reduce IOP (266,267,268) but these means of delivery have serious drawbacks including short duration of cannabinoid action (3-4 h) and unwanted physical and psychotropic effects. An endocannabinoid system exists in a number of ocular tissues and post-mortem studies have detected decreased levels of endocannabinoids in such tissues taken from glaucoma patients (269). Ocular (as well as systemic) administration of cannabinoids typically lowers IOP by up to 30% (see (264) for a full reference list). How cannabinoids reduce IOP is unclear, but several possible mechanisms have been proposed including reduction of capillary pressure, decreased aqueous humour production and improved aqueous humour uveoscleral outflow and outflow facility (270,271,272,273,274). A well-controlled pilot study reported that sublingual doses of 5 mg THC significantly but temporarily reduced IOP, while 20 mg cannabidiol (CBD) had no effect and 40 mg of CBD caused a transient increase in IOP (275). A non-randomized, uncontrolled study reported some improvement in IOP in patients with end-stage, open-angle glaucoma taking oral THC (2.5 or 5 mg q.i.d. up to a maximum of 20 mg/day) however patients appeared to develop tolerance to the ocular effects of THC and almost half discontinued treatment due to THC-associated toxicity (276). Aside from lowering IOP, cannabinoids such as

THC and CBD may also have neuroprotective effects which could also be useful in the management of glaucoma (277,278,279,280,281,282,283,284,264,285,286). These benefits notwithstanding, neither the American Glaucoma Society nor the Canadian Ophthalmological Society recommend the use of cannabinoids for the treatment of glaucoma at this time due to the availability of other therapeutic options and the current inability to separate the potential clinical action of marijuana from its undesirable neuropsychological and behavioural effects (265,287).

4.6.3 Asthma

There is historical and anecdotal evidence for marijuana as a treatment for asthma (288). Clinical studies have demonstrated significant decreases in airway resistance and increases in specific airway conductance in healthy, habitual marijuana smokers shortly after smoking marijuana (289,290) and this effect has been largely attributed to the bronchodilatory properties of THC (291). For asthmatics, the benefits of smoking marijuana are likely to be minimal. While smoking marijuana appears to decrease bronchospasm, increase bronchodilation and modestly improve respiratory function in some asthmatics in the short-term (292,293,294), marijuana smoke contains noxious gases and particulates that irritate and damage the respiratory system (291); hence it is not a viable long-term therapy for asthma. Alternate methods of THC delivery by aerosol or oral administration have also been studied. 100 and 200 µg of aerosolized THC significantly improved ventilatory function in asthmatics and was generally well tolerated (295,296). In another study, 5-20 mg of aerosolized THC rapidly and effectively increased airway conductance in healthy subjects but caused either bronchodilation or bronchoconstriction in asthmatics (297). Oral administration of 10 mg THC or 2 mg nabilone did not produce clinically significant bronchodilation in patients with reversible airways obstruction (298,288,299). Although animal studies with classical and synthetic cannabinoids suggest a promising role for cannabinoid-based compounds in the treatment of asthma (300,301,302), cannabinoids are not currently indicated for this condition.

4.6.4 Hypertension

CB₁ receptors are expressed on various peripheral tissues including the heart and vasculature, and cannabinoid agonists and endocannabinoids decrease arterial blood pressure and cardiac contractility (reviewed in (303)). Very few studies on the effects of marijuana on hypertension exist. Inhalation of marijuana with 2.8% THC caused a greater and longer-lasting decrease of arterial blood pressure in hypertensive subjects compared to normotensives (304). In one case report, a woman with longstanding idiopathic intracranial hypertension reported improvement in her symptoms after smoking marijuana or treatment with dronabinol (10 mg b.i.d initially, then 5 mg b.i.d.). Although cannabinoids may have a role to play in attenuating hypertension, tolerance to the cardiovascular effects along with the well-known adverse physical and psychotropic effects would preclude their consideration as a long-term treatment in hypertension (2).

4.6.5 Psychiatric disorders

There are anecdotal and historical claims regarding the beneficial effects of cannabis in the treatment of anxiety, depression, and sleep disorders, as well as for the treatment of alcohol and opiate withdrawal symptoms (305). However, insufficient clinical evidence exists at this time to recommend the use of cannabinoids in the treatment of such disorders.

Results from animal studies suggest low doses of CB₁ receptor agonists or inhibitors of the enzyme fatty acid amide hydrolase (FAAH), which degrades anandamide, reduce anxiety-like behaviour and increase antidepressant-like responses. On the other hand, high-level stimulation of the CB₁ receptor or administration of CB₁ receptor antagonists elicit opposite responses (306,307,308,309). CB₁ receptor agonists and FAAH inhibitors appear to enhance central serotonergic and noradrenergic transmission similar to the actions of antidepressant medications (306,310).

Clinical trials of marijuana or oral THC to treat anxiety or depression show either a lack of improvement or worsening of the condition (311,312,313,314). More recently, a number of studies have suggested an association between cannabis use and the development of psychosis, especially in people susceptible to psychotic disorders as well as in adolescents (315,316,317,318,319). A population-based, 13-year longitudinal study has suggested an association between exposure to cannabis and protracted suicidal thoughts or attempts in young Norwegians (320). On the other hand, preliminary evidence suggests that cannabidiol (CBD) may have anti-psychotic (321) and anxiolytic (322) activity.

Anecdotal information and some animal studies suggest that cannabinoids may be useful in treating the symptoms associated with opiate withdrawal (323,324,325) but no clinical studies support this indication (2).

4.6.6 Alzheimer's disease and dementia

Although increasing evidence from pre-clinical and clinical studies suggests a potential therapeutic role for cannabinoids in Alzheimer's disease (AD), there is insufficient clinical evidence at this time to support the use of cannabinoids in this regard.

Results from *in vitro* studies suggest cannabinoids reduce the neurotoxic effects associated with the deposition of A β plaques (reviewed in (326)). One study performed in a rat model of AD suggested the synthetic cannabinoid WIN 55,212-2 could exert a neuroprotective function (327). A double-blind, placebo-controlled, 6-week crossover study of 12 patients suffering from Alzheimer-type dementia reported 5 mg of dronabinol daily was associated with a decrease in disturbed behaviour (328). Adverse reactions such as fatigue, somnolence and euphoria were reported in dronabinol-treated patients. One open-label pilot study of 6 patients suggested an evening dose of 2.5 mg dronabinol reduced nocturnal motor activity and agitation in those who were severely demented (329).

4.6.7 Inflammation

The ability of cannabinoids to suppress the production of pro-inflammatory cytokines and chemokines has been well-documented and may have therapeutic applications in diseases with an underlying inflammatory component (330,331).

4.6.7.1 Inflammatory bowel disease (Crohn's disease, colitis)

Although there are no reports of clinical trials of cannabinoids for the treatment of inflammatory bowel disease (IBD), anecdotal evidence suggests that patients suffering from IBD may experience symptomatic relief by smoking marijuana. Cannabinoid receptors are expressed in the enteric nervous system, in human colonic epithelium and in a number of colonic epithelial cell lines (332,333). Furthermore, cannabinoids appear to have many functions in the digestive system including regulating gastric acid production, gastrointestinal motility, secretion and ion transport, and visceral sensation and inflammation (reviewed in (334)). Intestinal biopsies taken from patients with IBD including ulcerative colitis, Crohn's disease, diverticulitis, and celiac disease show increased CB receptor expression and/or enhanced endocannabinoid levels (335,332,336,337). Pre-clinical experiments in animal models of IBD suggest cannabinoids and endocannabinoids may limit intestinal inflammation via activation of CB receptors (338,339,340,341,342,343). Although the results from such studies are encouraging, further research is required to determine if cannabinoids are beneficial in IBD patients.

4.6.7.2 Inflammatory skin diseases (dermatitis, psoriasis, pruritus)

The skin possesses an endocannabinoid system (ECS) (344). CB₁ and CB₂ receptors are expressed in a number of skin cells including epidermal keratinocytes, cutaneous nerves and nerve fibres, sebaceous cells, myoepithelial cells of eccrine sweat glands and sweat gland ducts, mast cells and macrophages (345). In addition, elements of the ECS have been detected in human epidermal keratinocytes (346). The ECS appears to regulate the balance between keratinocyte proliferation, differentiation and apoptosis; it may therefore play a role in cutaneous homeostasis and in diseases such as psoriasis, which is characterized by keratinocyte proliferation and inflammation (346,347,344).

The results from pre-clinical studies on the role of cannabinoids in the modulation of cutaneous allergic reactions are mixed. Some studies suggest a protective role for cannabinoids while others, an antagonistic one (reviewed in (344)). In clinical studies, experimentally-induced, histamine-triggered pruritus was reduced by peripheral administration of the cannabinoid receptor agonist HU210, and the accompanying increases in skin blood flow and neurogenic mediated flare responses were attenuated (348). In another study, topically applied HU210 significantly reduced the perception of pain in human subjects following administration of capsaicin and reduced heat hyperalgesia and touch-evoked allodynia without any psychomimetic effects (349). Thus, it is possible that cannabinoids have therapeutic value in the treatment of certain inflammatory skin conditions (such as psoriasis, pruritus, and dermatitis), but further research is required. On the other

hand, there have also been some case reports of contact urticaria following exposure to cannabis flowers, and extreme sensitization to THC and cannabinoil has also been documented in an animal model of contact dermatitis (350,351).

4.6.8 Bladder dysfunction

Bladder dysfunction occurs in most patients suffering from multiple sclerosis (MS) or spinal cord injury (352). The most common complaints are increased urinary frequency, urgency, urge and reflex incontinence (353). Cannabinoid receptors are expressed in human bladder detrusor and urothelium (354,355) and may help regulate detrusor tone and bladder contraction as well as affecting bladder nociceptive response pathways (reviewed in (355)).

A survey of MS patients regularly using cannabis for symptomatic relief of urinary problems reported that over half claimed improvement in urinary urgency (356). A 16-week, open-label pilot study of cannabis-based extracts (Sativex[®] followed by 2.5 mg THC only) for bladder dysfunction in 15 patients with advanced MS showed significant decreases in urinary urgency, number and volume of incontinence episodes, frequency and nocturia (357). Improvements were also noted in patient self-assessments of pain and quality of sleep. A subsequent randomized controlled trial of 250 MS patients suggested a clinical effect of orally administered cannabis (2.5 mg THC or 1.25 mg cannabidiol (CBD) with <5% other cannabinoids per capsule up to a maximum 25 mg/day) on incontinence episodes (352).

4.6.9 Anti-neoplastic properties

Results from *in vitro* and animal studies suggest cannabinoids and endocannabinoids inhibit tumour growth and the progression of several types of cancer including glioma, glioblastoma multiforme, breast, prostate, thyroid, colon carcinoma, leukemia, and lymphoid tumours (reviewed in (358,359)). Cannabinoid agonists appear to have a bi-modal mechanism of action with low concentrations being pro-proliferative and high concentrations having anti-proliferative effects (358).

There is only one report of a clinical study of THC to treat cancer (360). In this pilot study, nine patients with glioblastoma multiforme who had failed standard surgical and radiation therapy, had clear evidence of tumour progression, and had a minimum Karnofsky score of 60 were treated with 20-40 µg THC intracranially per day (with doses up to 80-180 µg per day). Median treatment duration was 15 days (360). While intracranial administration of THC appeared to be well tolerated, the effect of THC on patient survival was unclear. Nevertheless, *in vitro*, THC inhibited the proliferation and decreased the viability of tumour cells isolated from glioblastoma biopsies most likely through a combination of cell-cycle arrest and apoptosis (360,359). A more recent *in vitro* study suggests that CBD enhances the inhibitory effects of THC on human glioblastoma cell proliferation and survival (359).

5.0 Contraindications

The contraindications that apply to those considering using Sativex[®] or Marinol[®] also apply to the use of marihuana. Marihuana is contraindicated in any person under the age of 18 as well as any patient who has a history of hypersensitivity to any cannabinoid or to smoking. Marihuana should not be used in patients with liver, kidney or cardio-pulmonary disease, or a history of psychiatric disorders, particularly schizophrenia. It is also contraindicated in women of childbearing age not on a reliable contraceptive, as well as those planning pregnancy, those who are pregnant or women who are breastfeeding. Men intending to start a family are also discouraged from using marihuana. Marihuana may also exacerbate the CNS depressant effects of sedatives, including alcohol. Concomitant use of marihuana with other drugs may increase the incidence of adverse effects (see section 7.3).

6.0 Warnings

The dose of marihuana to be smoked is difficult to estimate and is affected by the source of the plant material, its processing and by different smoking techniques. These include depth of inhalation and breath-holding and the 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 experience the following effects: disorientation, dizziness, ataxia, agitation, anxiety, tachycardia and orthostatic hypotension, depression, hallucinations, psychosis.

Marihuana is one of the most widely abused illicit drugs, can produce physical dependence and has the potential to be addictive (361,362). The drug has complex effects in the CNS and can cause cognitive and memory impairment, changes in mood, altered perception and decreased impulse control (363,364,365,366). Patients should be supervised when administration is initiated.

Any patient experiencing a psychotic reaction to marihuana should stop taking the drug immediately and be kept under observation until the 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 (367). Such impairment can last for over 24 h after last use because of the long half-life of THC.

Pregnancy: Use of marihuana during pregnancy should be avoided as there is some evidence of long-term developmental problems in children exposed to marihuana *in utero* (368,369).

Lactation: Cannabinoids are excreted in human milk and may be absorbed by the nursing baby (370,371). 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, 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 of the negative effects on memory and to report any mental or behavioural changes that occur after using marihuana.
- Patients with ongoing chronic hepatitis C should be strongly advised to abstain from daily cannabis use, as this has been shown to be a predictor of steatosis severity in these individuals (372).

7.2 Dependence and withdrawal

Tolerance, psychological and physical dependence can occur with prolonged use of marihuana (27,373). Tolerance to cardiovascular effects occurs quickly, but the dependence is slower to develop and appears more likely with higher, more frequent dosing (374,375).

7.3 Drug interactions

The most clinically significant interaction may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol. Some studies have reported enhanced CNS depressant effects when marihuana and alcohol are used in combination (376,377).

Substances that inhibit CYP isoenzymes 2C9 and 3A4 such as macrolides (clarithromycin and erythromycin), antimycotics (itraconazole, fluconazole, ketoconazole, miconazole), calcium antagonists (diltiazem, verapamil), HIV protease inhibitors (ritonavir), amiodarone and isoniazid can increase the bioavailability of THC as well as the chance of experiencing THC-related side-effects (52). Drugs that accelerate THC metabolism via 2C9 and 3A4 isozymes such as rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone, and Saint John's Wort may conversely decrease the bioavailability of THC and hence, its effectiveness if used in a therapeutic context (52). THC,

CBD, and CBN inhibit CYP isozymes such as CYP1A1, 1A2 and 1B1 (83). Cannabis may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitriptyline, phenacetin, theophylline, granisetron, dacarbazine, and flutamide (83). Patients taking fentanyl (or related opioids) and antipsychotic medications (clozapine or olanzapine) may also be at risk of experiencing adverse effects (86,85,87). Clinicians should therefore be aware of other medications that the patient is taking and carefully monitor patients using these drugs along with cannabis or cannabinoids.

7.4 Drug screening tests

Because of the long half-life of elimination of cannabinoids and their metabolites, drug tests screening for cannabinoids can be positive weeks after last marijuana use (378,379).

8.0 Adverse Effects

8.1 Carcinogenesis and mutagenesis

While there are many cellular and molecular studies that provide strong evidence that smoked marijuana is carcinogenic (reviewed in (27)), the epidemiological evidence of a link between marijuana use and cancer is still inconclusive. One epidemiological study in relatively young health maintenance organization (HMO) clients found an increased number of men with prostate cancer in those who smoked cannabis and other non-tobacco materials (380). No other associations were found between marijuana use and other cancers however the study was limited by the demographics of the HMO clientele and the low marijuana exposures. A case-control study suggested that marijuana use may increase the risk of head and neck cancer (OR 2.6; CI 1.1-6.6) with a strong dose-response pattern compared to non-smoking controls (381). The authors note a number of limitations with their study such as underreporting, inaccurate marijuana dose reporting, assay sensitivity and low power. A large 2006 population-based case-control study of 1,212 incident cancer cases and 1,040 cancer-free matched controls did not find a significant relationship between long-term cannabis use and cancers of the lung and upper aerodigestive tract (382). However, a smaller 2008 case-control study in young adults (≤ 55 years of age) examining 79 cases of lung cancer and 324 controls reported that the risk of lung cancer increased 8% (95% CI 2-15%) for each joint-year of cannabis smoking after adjusting for cigarette smoking (383).

8.2 Respiratory tract

Mucosal biopsy specimens taken from chronic marijuana smokers who reported only smoking marijuana showed a number of histopathologic changes including basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia (384). However, the study employed a small number of subjects and relied on the accuracy and integrity of the subjects' recall to establish smoking status, as well as frequency and duration of smoking. Epidemiological studies have found mild changes in pulmonary function in heavy cannabis smokers, including reduction of forced expiratory volume in 1 second (FEV₁), increase in airway resistance and decrease in airway conductance (385,13,386). Heavy chronic cannabis smokers presented with symptoms of bronchitis, including wheezing, production of phlegm and chronic cough and long-term cannabis smoking may be a risk factor for chronic obstructive pulmonary disease in later life (30,387). All changes were most evident in heavy chronic users, defined as those who smoked more than 3 joints per day for 25 years (380,388). The effects on the respiratory tract defence system may increase the risk of infection in chronic users (389) however further epidemiological research is required to establish a causal relationship between marijuana smoking and respiratory infection.

8.3 Immune system

Cannabinoids appear to have powerful anti-inflammatory and immune-suppressive properties (390), however, the effects of marijuana smoking on the immune system in humans are less clear. A major concern with HIV-positive marijuana smokers is that they might be more vulnerable than other marijuana smokers to the immunosuppressive effects of marijuana or that they risk exposure to infectious organisms associated with marijuana plant material (116). A group of studies has partially addressed the former concern. In one study, HIV-positive patients on stable antiretroviral therapy randomized to smoked marijuana or dronabinol showed no changes in CD4+ and CD8+ T-cell, B cell, or NK cell counts and a number of other parameters compared with placebo over a 21-day study period (391). A longitudinal study of 481 HIV-infected men who used marijuana and who were followed over an average 5-year period found that while marijuana use was generally associated with a higher CD4+ cell count in infected men and

controls, no clinically meaningful associations, adverse or otherwise, between marijuana use and T-cell counts and percentages could be established (392). Marijuana use was also not associated with an increased rate of progression to AIDS in HIV-infected individuals (393). In another study, smoking marijuana was associated with lower plasma concentrations of the protease inhibitors (PI) indinavir and nelfinavir; dronabinol or placebo had no effect (85). However, the decreased PI levels were not associated with an elevated viral load or changes in CD4+ or CD8+ cell counts (132). Nevertheless, results from *in vitro* and *in vivo* experiments in animals suggest cannabinoids have an impact on virus-host cell interactions (394); cannabinoid treatment was associated with increased viral replication of HSV-2, HIV-1, KSHV, influenza, and VSV viruses or with increases in surrogate measures of infection in these models (395,396,397,398,399,400). In humans, smoking marijuana was associated with poorer outcome in patients with chronic hepatitis C (401,402). Caution should also be exercised when prescribing marijuana to patients undergoing cancer chemotherapy and whose immune systems may be compromised (116).

8.4 Reproductive and endocrine systems

Results from human epidemiological studies examining short-term neonatal outcomes among women who smoked cannabis during pregnancy are equivocal; some report reduced neonatal birth weight and length (403,404,405,406) or a slightly increased risk of sudden infant death (407), while others report no effect (408,409,410). On the other hand, there appear to be some long-term effects on the development of children born to mothers who used marijuana during pregnancy. Two longitudinal investigations over 20 years (reviewed in (368)), and confirmed by a third (369), suggest that such *in utero* exposure impacts negatively on attentional behaviour and visual analysis and hypothesis testing but not on standardized derived IQ scores. These behavioural effects also appeared to have a negative influence on aspects of executive function in later years.

Evidence suggests that cannabinoids accumulate in the breastmilk of mothers who smoke cannabis and are transferred to newborns through breastfeeding (370,411). In a case-control study (412), exposure to marijuana 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.

The effects of marijuana and THC on human sperm have been investigated both *in vivo* and *in vitro* (413,414,415). A significant decline in sperm count, concentration and motility and an increase in abnormal sperm morphology were observed in men who smoked marijuana (8-20 cigarettes/day) for 4 weeks (413). In an *in vitro* study, sperm motility and acrosome reactions were decreased in both the 90% and 45% sperm fractions; the 90% fraction being the one with the best fertilizing potential and the 45% fraction being a poorer subpopulation (415). Decreased sperm motility was observed in both fractions at THC concentrations mimicking those attained recreationally (0.32 and 4.8 μM) and in the 45% fraction at THC concentrations typically seen therapeutically (0.032 μM). Inhibition of the acrosome reaction was only observed at the highest THC concentration tested (4.8 μM) in the 90% fraction while the 45% fraction displayed decreased acrosome reactions at all three THC concentrations. Such effects carry the possibility of impairing crucial sperm functions and male fertility, especially in those males already on the borderline of infertility (415).

8.5 Cardiovascular system

The most consistent acute physiological effect of smoking marijuana is dose-related tachycardia (416). While this is not usually considered dangerous for healthy young users, it may be problematic to those already suffering from cardiac disorders or angina (27). Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50% (417) and has been associated with an increased relative risk of nonfatal myocardial infarction in the first hour following smoking (418). This may be caused by a THC-related increase in cardiac output, myocardial oxygen demand, catecholamine levels, carboxyhemoglobin as well as postural hypotension (416,419,420). While tachycardia is observed in both occasional and chronic users, tolerance develops relatively quickly with the degree of tachycardia diminishing with use. After about 8 to 10 days of constant dosing with 10 mg of THC per day (equivalent to 80-100 mg of marijuana containing 10% THC), bradycardia with a decrease in supine blood pressure was observed (421).

Cannabis is also known to cause peripheral vasodilation, postural hypotension, and characteristic conjunctival reddening after smoking (422).

AIDS patients may be at an increased risk of experiencing adverse cardiovascular outcomes caused by interactions between cannabis and antiretroviral drugs, such as ritonavir, which has been associated with adverse cardiovascular events (423).

8.6 Liver

Recent studies have strongly implicated the endocannabinoid system in chronic liver disease (424,425,426,427,428). Studies in patients with chronic hepatitis C, found a significant association between daily cannabis smoking and moderate to severe fibrosis (402), as well as being a predictor of fibrosis progression (401). Another study showed that daily cannabis use was a predictor of steatosis severity in these individuals (372). Steatosis is an independent predictor of fibrosis progression and an established factor of poor response to antiviral therapy (429). The authors recommend that patients with ongoing chronic hepatitis C be strongly advised to abstain from daily cannabis use. In contrast, a study by Sylvestre et al. (430), showed that modest cannabis use (defined as anything less than daily use) may offer symptomatic and virological benefit to some patients undergoing hepatitis C treatment.

8.7 Central nervous system

The most frequently reported adverse events for cannabinoids involve the central nervous system (CNS). Commonly encountered CNS events in controlled clinical trials with Marinol[®] and Sativex[®] are intoxication-like reactions including drowsiness, dizziness and transient impairment of sensory and perceptual functions (53,55). A “high” (easy laughing, elation, heightened awareness) from Marinol[®] was reported in 24% of the patients receiving it as an antiemetic and in 8% of patients receiving it as an appetite stimulant (53). Dizziness is the most common intoxication effect with Sativex[®] reported initially in 35% of patients titrating their dose; the reported incidence of this effect in long-term use is approximately 25% (431). All other intoxication-like effects are reported by less than 5% of users (with the exception of somnolence 7%) (431). Other events reported for Sativex[®] include disorientation and dissociation. CNS events for Marinol[®] also include paresthesias, visual distortions (all at 3%), paranoia, depersonalization (each 2%) and disorientation with confusion (1%) (55).

8.7.1 Cognition

The effects of cannabis use on cognition have been reviewed by Lundqvist (432). Marijuana impairs cognition involving short-term memory, attention, concentration, executive functioning and visuosperception (433,365,434). The digit span task has been used to estimate the effects of cannabis on recent memory, but results have been inconsistent. Differences may be due to the dosage used, the smoking procedure or whether the digit span task assesses forward or backward recall (435). Cannabis intoxication significantly impairs the ability to learn and recall word lists or short stories (436).

The long-term effects of cannabis on cognition remain controversial. Some studies report a positive association between cannabis consumption and cognitive deficits (437,438,439) or suggest that cognitive deficits persist after abstinence (440,441,433,365), whereas others did not find an association between cannabis use and long-term cognitive decline (440,441). Methodological limitations and the absence of powerful effects have contributed to difficulties in assessing the effects of chronic use and may help explain the discrepancies among studies (442,443). Nonetheless, studies generally suggest that chronic users of marijuana suffer varying degrees of cognitive impairment that have the potential to be long-lasting (35).

8.7.2 Psychomotor performance

Cannabis exposure impairs psychomotor performance (27) and patients must be warned not to drive after smoking marijuana. A double-blind, placebo-controlled, crossover study comparing the effects of a medium dose of dronabinol (20 mg) and of two hemp milk decoctions containing medium (16.5 mg) or high doses (45.7 mg) of THC reported severe impairment on several performance skills required for safe driving (444). Performance impairment appears to be less significant among heavy cannabis users compared to occasional users (27). It has been suggested that, unlike alcohol, cannabis users are aware of their level of intoxication and compensate by becoming hyper-cautious; in tasks such as driving this kind of behaviour results in decreased speed, decreased frequency of overtaking, and an increase in following distance (445,446). Others disagree with this assertion (447). In any case, individuals are affected differently by prolonged exposure to marijuana and there is some evidence of greater psychomotor effects on adolescents (448).

8.7.3 Psychiatric effects

8.7.3.1 Acute reactions

Cannabis use has been linked to episodes of acute psychosis in both regular and drug-naïve users. Two case reports of healthy subjects who had participated in a randomized controlled trial (RCT) measuring the effects of orally administered cannabis (including dronabinol or cannabis decoctions) on psychomotor performance displayed acute psychotic reactions following exposure to cannabis (449). The subjects had no psychiatric history or concomitant drug use but were “occasional” regular cannabis users. In another RCT, 22 healthy subjects also with a history of occasional cannabis use, no concomitant drug use, and with no psychiatric disorders received intravenous doses of Δ^9 -THC paralleling peak plasma THC levels achieved by smoking cannabis cigarettes containing 1-3.5% Δ^9 -THC (450). Drug administration was associated with a range of acute, transient, behavioural and cognitive effects including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and illusions. Depersonalization, derealization, distorted sensory perceptions, altered bodily perceptions, feelings of unreality and extreme slowing of time were also reported. Furthermore, blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and emotional withdrawal were observed. Another study reported similar results (451). Similar short-term psychotic reactions have also been documented in some naïve cannabis users (452,30,449).

8.7.3.2 Depression

While the link between the use of marijuana and depression is a growing area of concern, research on this topic is relatively scarce and conflicting. A 2003 review reported that the comorbidity level between heavy or problematic cannabis use and depression in surveys of the general population exceeds what would be expected by chance (453). The authors also identify a modest association between early-onset regular or problematic use and later depression. However, limitations in the available research on cannabis and depression, including study design, as well as the measurement of cannabis use and depression were also highlighted. A U.S. study of adults (454) using longitudinal national survey data (n= 8 759) found that the odds of developing depression in past-year marijuana users was 1.4 times higher than the odds of non-users developing depression. However, after adjusting for group differences, the association was no longer significant. In a 2008 study, the same group looked at the relationship between cannabis use and depression among youth using a longitudinal cohort of 1 494 adolescents. Similar to the adult study, the results did not support the causal relationship between adolescent-onset cannabis use problems and early adult depression (455). In contrast, another U.S. study (456) based on the results of the National Epidemiological Survey on Alcohol and Related Conditions (n= 43 093), found major depression was significantly associated with lifetime cannabis disorders and dependence. A 2007 study using data from the Netherlands Mental Health Survey and Incidence Study did find a modest increased risk of a first depressive episode (OR 1.62; 1.06-2.48) after controlling for strong confounding factors (457). Of greater significance in this study, was the strong increased risk of bipolar disorder (OR 4.98; 1.80-13.81) with cannabis use. There was a dose-response relationship associated with the risk of ‘any mood disorder’ for almost daily and weekly users but not for less frequent users. A survey of 248 French high school students found cannabis users had significantly higher rates of suicidal behaviours, depressive and anxious symptoms compared to cannabis non-users (458). In conclusion, while a relationship between cannabis and depression may exist, more studies are needed to establish a causal relationship.

8.7.3.3 Schizophrenia and psychosis

Individuals with schizophrenia or with a family history of this disorder are likely to be at greater risk of suffering adverse psychiatric effects from marijuana (364). Interestingly, genetic studies indicate a link between allelic variants of the cannabinoid receptor gene (CNR1) and susceptibility to mood disorders (459,460). Heavy marijuana use can aggravate psychotic symptoms and cause more relapses and those who use marijuana are at an increased risk of a poor prognosis (461,462,315,27). Self-reported use of cannabis in adolescence has been associated with an increased risk of developing schizophrenia and this risk was related to frequency of marijuana exposure (463). A cohort study of over 1000 children, followed from birth to age 26, reported a three-fold increased risk of psychotic disorders in those who used cannabis and suggested that cannabis exposure among psychologically vulnerable adolescents should be strongly discouraged

(464). The relationship between cannabis use and psychotic symptoms was also studied in a cohort of 2 437 young people (14-24 years) with greater than average predisposition for psychosis and who had first used cannabis during adolescence (465). The authors found a dose-response relationship between frequency of cannabis use and the risk of psychosis. The effect of cannabis use was also much stronger in those individuals with a predisposition for psychosis. Although cannabis use increases the risk of psychosis, it is only one factor in a larger constellation of contributing factors (466). A systematic review of evidence pertaining to cannabis use and the occurrence of psychotic or affective mental health outcomes reported an increased risk of any psychotic outcome in individuals who had ever used cannabis compared with non-users (OR = 1.41) (317). Furthermore, the findings appeared to show a dose-related effect, with greater risk to individuals who used cannabis most frequently (OR = 2.09).

8.7.3.4 Amotivational syndrome

This syndrome is used to describe people who show little interest in school, work or other goal-oriented activity as well as withdrawing from social activities (27). To date, there is no convincing evidence to show a causal relationship between marijuana use and such behavioural characteristics (27). Rather, it appears that this constellation of behaviours is the result of chronic cannabis intoxication; de-intoxication results in resolution of symptoms (364,467).

8.8 Tolerance and dependence

Tolerance to most of the effects of marijuana can develop after a few doses and it also disappears rapidly following cessation of administration (27). In normal subjects, tolerance develops to the effects of marijuana on mood, intraocular pressure, EEG, psychomotor performance, nausea as well as on the cardiovascular system (468,469). The dynamics of tolerance vary with respect to the different effects; tolerance to some of the effects develops more readily and rapidly than others (470). In one study, tolerance to some of the cannabis effects developed both when THC was administered orally (30 mg four times a day) and when a roughly equivalent dose was given by smoking (3.1% cigarette; 5 puffs of 10 seconds each) (471). While both groups became tolerant to the "high", there was no diminution of the appetite stimulating effect from either route of administration.

There is evidence that cannabis dependence occurs with chronic heavy use (30,373). In the DSM-IV-TR, the term 'dependence', is closely related to the concept of addiction which may or may not include physical dependence and is characterized by use despite harm and loss of control over use (472). Physical dependence may also occur resulting in withdrawal symptoms when use is discontinued. Withdrawal symptoms appear within the first one to two days following discontinuation of cannabis use (smoked or oral), peak effects typically occur between days 2 and 6 and most symptoms resolve within 1-2 weeks (473). The most common symptoms include anger or aggression, irritability, anxiety, restlessness, decreased appetite or weight loss, and sleep difficulties. Less common symptoms include depressed mood, chills, stomach pain, shakiness and sweating.

9.0 Overdose/Toxicity

LD₅₀ values for rats administered single oral doses of THC or crude marijuana extract are approximately 1000 mg/kg (474). Dogs and monkeys are able to tolerate significantly higher oral doses of THC or marijuana extract of 3000 mg/kg (or greater in certain cases) (474). The estimated human lethal dose of intravenous THC is 30 mg/kg (2100 mg/70 kg) (53). Significant CNS symptoms are observed with oral doses of 0.4 mg/kg Marinol[®] (53). Cannabis often produces unwanted physical effects, typically dizziness, sedation, intoxication, clumsiness, dry mouth, lowered blood pressure or increased heart rate (475). These adverse effects are generally tolerable and not unlike those seen with other medications (27). The rare acute complications (such as panic attacks, psychosis, convulsions, etc.) that present to the Emergency Department can be managed with conservative measures (476). As is stated in the case of overdose with Marinol[®] (53), the signs and symptoms observed with smoked marijuana 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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