

Information for Health Care Professionals  
(Revised)

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

Psychoactive agent

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

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

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

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

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## **1.0 Chemistry**

### **1.1 Composition**

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

Although the leaves and flowering tops of *Cannabis* plants yield more than 60 cannabinoids, the major active components are  $\Delta^9$ -THC, cannabinol (CBN) and cannabidiol (CBD) (British Medical Association, 1997, p 7).

### **1.2 Other ingredients**

There are other components in marihuana joints which are common to tobacco and the smoke from them is considered chemically similar to that from tobacco cigarettes (Iverson, 2000, p 191; British Medical Association, 1997, p 14). However, some investigators report that two potent carcinogens in tobacco smoke, benzanthracene and benzpyrene, are present in higher amounts in marihuana smoke (Novotny, et al., 1976). Differences in the smoking techniques used by marihuana and tobacco smokers are reported to result in three-fold higher levels of tar and five-fold higher levels of carbon monoxide being retained in the lungs during cannabis than during tobacco smoking (Wu, et al., 1988). This greater retention of tar and carbon monoxide from cannabis smoke may offset 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) (Peterson, 1979; Tashkin, et al, 1987).

### **1.3 Stability and storage**

Most of the information on stability of marihuana does not distinguish between THC and its carboxylic acid analogue (THCA). The latter is degraded to THC by pyrolysis during smoking or in the inlet of gas chromatographs used in forensic analysis (Baker, et al., 1981). Heat, light, humidity, acidity and oxidation all affect the stability of cannabis (Garrett, et al., 1974; Mechoulam, et al., 1981). Available information suggests that THC in recently harvested plant material stored in dry, tightly- closed, refrigerated containers would be stable for several months. The National Institute of Drug Abuse (NIDA) reports (Thomas, et al., 1999) that retention samples of their carefully prepared and standardized cigarettes are stable for months, particularly when stored below 0°C. However, even at 18°C, there is a loss of only a third of the THC potency (from 2.87 to 1.8% THC) over 5 years, with some increase in the concentration of CBN.

## **2.0 Clinical Pharmacology**

### **2.1 Pharmacodynamics**

Most of the pharmacodynamic information on marihuana in humans refers to the effects of the major constituent THC. CBD does not appear to be psychoactive; its principle

action is inhibition of cytochrome P450 enzymes, which decreases the metabolism of TCH and other drugs. CBN, while only weakly active compared to THC in the brain, appears to have activity in isolated immune cells (National Academy of Sciences, 1999, p 2.5).

Cannabinoid receptors have been discovered in neural tissue. Two types of cannabinoid receptors, CB1 and CB2, have been identified. Table 1, adapted from the British Medical Association Report (British Medical Association, 1997, p 19), notes some of the effects of cannabis. Many of the effects are biphasic, e.g., increased activity with acute or smaller doses, decreased activity with larger doses or chronic use. Effects differ greatly among individuals and may be greater in severely ill and elderly patients.

<b>Table 1: Pharmacologic actions of cannabis in man</b>	
<b>Body System/Effect</b>	<b>Detail of Effects</b>
<b>CNS</b>	
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 demanding tasks.
Motor function	Increased motor activity followed by inertia and in coordination, ataxia, dysarthria, tremulousness, weakness, muscle twitching.
Analgesic	Currently available oral cannabinoids are similar in potency to codeine (but from a different mechanism).
Anti-emetic, increased appetite	With acute doses; effect reversed with larger doses or chronic use (tolerance).
Tolerance	To most behavioural and somatic effects, including the “high”.
Dependence, abstinence syndrome	Has been produced experimentally following prolonged intoxication: symptoms include disturbed sleep, decreased appetite, restlessness, irritability and sweating. Information from therapeutic use lacking.
<b>Cardiovascular System</b>	
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.
<b>Respiratory system</b>	
Ventilation	Small doses stimulate; larger doses depress.
Bronchodilation	Coughing, but tolerance develops.
Airways obstruction	From chronic smoking.
<b>Eye</b>	Decreased intraocular pressure.
<b>Immune system</b>	Chronic use: impaired bactericidal activity of macrophages in lung and spleen.
<b>Reproductive System</b>	
Males	Antiandrogenic, decreased sperm count and sperm motility (chronic use, but tolerance may develop).
Females	Suppression of ovulation, complex effects on prolactin secretion; chronic use: increased obstetric risk.

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 (see Table 1) reach a plateau which can last for several hours. However, on first dosing, some people experience dysphoria and anxiety. The effects on the cardiovascular system (tachycardia, etc.) decline much faster as THC is distributed out of the circulatory system. Tachycardia is the most consistent of the physiological effects of marijuana (Beaconsfield, et al., 1972; Perez-Reyes, 1990).

The short-term psychoactive effects of marijuana smoking include euphoria, relaxation, time-distortion, perception of enhanced sensory experiences (such as music) and loss of inhibitions that may result in laughter (Hall, et al., 1998). This is followed by a depressant period (Ameri, 1999). While there is some inconsistency in reports of the acute effects on memory and motor skills (Fant, et al., 1998; Kelly, et al., 1993; Barnett, et al., 1985), most reviews note that marijuana use is associated with impaired function of a variety of cognitive tasks and short-term memory (Ameri, 1999; National Academy of Sciences, 1999, p 2.27; Hollister, 1998; Miller, Ch. 15 p 227-231). A major concern from such an acute effect is impairment affecting driving or operation of intricate machinery (Hansteen, et al., 1976; Smiley, et al., 1999; O’Kane, et al., 2002). There are reports of reduced skills on flight simulators by experienced pilots 24 h after smoking one marijuana cigarette (Leirer, et al., 1991). Plasma THC levels attained after smoking seem to have a dose and concentration dependent effect on cognitive function (Heishman, et al., 1990).

## **2.2 Pharmacokinetics**

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

### **2.2.1 Absorption**

#### **2.2.1.1 Smoked cannabis**

The estimation of dose administered by the smoking route is a major variable in the assessment of absorption of cannabinoids (mainly THC) in humans. The source of the plant material and the composition of the cigarette, together with the efficiency of smoking by the subject, are additional uncontrolled factors. It might be reasonable to consider about 10% (range 3-30%) as an average for THC content in Canadian marijuana. It appears that habitual (heavy) marijuana smokers can increase the amount absorbed, which is attributed to more efficient smoking techniques (Agurell, et al., 1986).

THC absorption by inhalation is extremely rapid, with a bioavailability of 18 to 50% from the cigarette (Huestis, 1999), and is the main reason this route is preferred by many people (Iverson, 2000, p 46-47).

Standardised cigarettes have been developed by 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 (Ohlsson, et al., 1980).

THC levels in plasma decreased rapidly after cessation of smoking and were below 5 ng/mL, 2 hours after smoking; mean concentrations declined by about 50%, 15 minutes after (Huestis, et al., 1992) reaching the maximum (Huestis, 1999). However, THC from a single dose can be detected in plasma for at least a day using modern sensitive analytical techniques and for 13 days in chronic users (Johansson, et al., 1988). The decline of THC in plasma is multiphasic and as Harvey (Harvey, 1999) notes, the estimates of the terminal half-life of THC in humans have increased as analytical methods have become more sensitive. There is still no consensus. It is probably safe to say that the terminal half-life of THC averages at least a week and could be considerably longer. The half-life in plasma does not appear to be different between heavy and light users (Aguirell, et al., 1971).

#### **2.2.1.2 Oral THC**

Absorption from an oral dose of 20 mg THC in a chocolate cookie was described as slow and unreliable (Aguirell, et al., 1986), with a systemic availability of only 4 to 12% (Ohlsson, et al., 1980). While most subjects had peak plasma THC concentrations between 1 to 2 hours, some of the 11 subjects only peaked at 6 hours and many had more than one peak.

Only 10-20% of synthetic THC (dronabinol, Marinol<sup>®</sup>) administered in capsules with sesame oil enters the systemic circulation indicating extensive first-pass metabolism (Compendium of Pharmaceuticals and Specialties, 2003). The psychotropic effect or “high” is observed to occur more quickly by the smoking than the oral route, which has been characterized by Iversen (Iversen, 2000, p 46-47) as the reason “smoking is the preferred route of cannabis for many people”.

#### **2.2.1.3 Rectal THC**

Limited evidence suggests a higher bioavailability of THC by the rectal route than by the oral route (Mattes, et al., 1993 p 745-747; Brenneisen, et al., 1996).

### **2.2.2 Distribution**

Distribution of THC begins immediately after absorption. The plasma protein binding of THC and its metabolites is approximately 97% (Garrett, et al., 1977; Widman, et al., 1974). THC is mainly bound to low-density lipoproteins, with up to 10% present in red blood cells (Walqvist, et al., 1970), while the metabolite, 11-hydroxy THC, is

even more strongly bound with only 1% found in the free-fraction (Widman, et al., 1973).

THC has a large apparent volume of distribution, approximately 10 L/kg, because of its high lipid solubility. Animal studies show that it is sequestered to fatty tissues including brain (Harvey, 1999). The highest concentrations are found in the heart and in adipose tissue, with levels reaching 10 and 1000 times that of plasma, respectively (Truitt Jr., 1971). THC readily crosses the blood brain barrier and the slight delay in correlating peak plasma concentration to effects is assumed to reflect this distribution (Agurell, et al., 1986). While immediate distribution is high in liver, spleen and body fat are the major sites of distribution after 72 h. Spleen and body fat are the long-term storage sites (Harvey, 1999).

There has been concern about the possible consequences of the long persistence of THC in fatty tissues. There is no evidence that the THC residues persist in the brain. Release from the fatty storage sites into blood is slow; levels attained are not high enough to cause psychological effects.

### **2.2.3 Metabolism**

Most metabolism of cannabinoids occurs in the liver and different metabolites predominate when different routes of administration are used. The complex metabolism of THC involves allylic oxidation, epoxidation, decarboxylation and conjugation (Agurell, et al., 1986). Cannabinoids are good substrates for cytochrome P450 mixed-function oxidases, mainly CYP 2C9. The major initial metabolites of THC are 11-hydroxy THC and 11-nor-9-carboxy THC. 11-hydroxy THC is rapidly formed by action of hepatic microsomal oxidases, and plasma levels parallel the duration of observable drug action. 11-hydroxy THC has been found to have psychotomimetic properties equal to THC (Christensen, et al., 1971; Perez-Reyes, et al., 1972).

#### **2.2.3.1 Inhalation**

After smoking (1.75 and 3.55% THC cigarettes) 11-hydroxy THC (Huestis, et al., 1992) appears rapidly and peaks shortly after THC, at about 15 minutes after the start of smoking. It exhibited peak plasma concentrations of about 7.5 ng/mL (about 5% of parent THC) and the AUC profile of this metabolite averaged 20% of the parent. Similar results were obtained with intravenous administration (Agurell, et al., 1971).

The psycho-inactive 11-nor-9-carboxy THC is the primary acid metabolite of THC excreted in urine (Huestis, et al., 1996) and it is the cannabinoid often screened for in forensic analysis of body fluids (Martin, et al., 1999). Peak plasma values of this metabolite occur 1.5 to 2.5 h after smoking and are about one third the concentration of parent THC. Following oxidation, the phase II

metabolites of the free drug or hydroxy-THC appear to be glucuronide conjugates (Aguirell, et al., 1986).

It is known that polyaromatic hydrocarbons found in tobacco and cannabis smoke induce the action of CYP1A2. If it is shown that the metabolism of THC also involves this cytochrome P450 isoenzyme, then repeated exposure to cannabis could cause the more rapid disappearance of THC via this specific enzyme (Valjent, et al., 2002). Various other cytochrome P450, enzymes are of interest for potential drug interactions. In human liver microsome preparations, CBD has been shown to inhibit formation of THC metabolites catalyzed by CYP 3A, with less effect on CYP 2C9 (Harvey, 1999). However, others suggest that CBD decreases formation of 11-hydroxy THC by inhibition of CYP 2C9 (Bornheim, et al., 1993). Observed and potential interactions of cannabis with other drugs are discussed later.

#### **2.2.3.2 Oral**

After oral doses of THC, parent THC and its active metabolite, 11-OH-THC, are present in approximately equal concentrations in plasma (Wall, et al., 1981; Cone, et al., 1988). Concentrations of both parent drug and metabolite peak at approximately 2 to 4 hours after oral dosing and decline over several days. Clearance averages about 0.2 L/kg-h, but is highly variable, due to the complexity of cannabinoid distribution (Marinol US monograph). The larger amount of 11-hydroxy THC metabolite, from first pass metabolism by this route, which is similar in potency to THC, complicates interpretation of potential effects. With oral THC dosing, the absorption is slow and variable, and peak concentrations of THC may be considered one tenth those from efficiently smoked administration but the plasma levels of active 11-hydroxy metabolite are about 3 times higher than observed in the plasma from smoking (Wall, et al., 1983).

#### **2.2.4 Excretion**

**Following inhalation,** elimination of THC and its metabolites occurs via the faeces (65%) and the urine (20%). After five days, 80% to 90% of the total dose is excreted.

Similarly, following oral doses, THC and its biotransformation products are excreted in both faeces and urine. Biliary excretion is the major route of elimination with about half of a radiolabelled oral dose being recovered from the faeces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the faeces. Following administration of a single oral dose, low levels of THC metabolites have been detected for more than 5 weeks in the urine and faeces (Harvey, 1999, p 91-103; Compendium of Pharmaceuticals and Specialties,2003).

Traces of marihuana can be detected in urine even for weeks (Ohlsson, et al., 1980) after dosing in forensic or employment situations when such testing may be applied.

### **2.3 Pharmacokinetic-pharmacodynamic relationships**

Though it is of major forensic interest, the temporal relationship between plasma concentrations of THC and its psychotropic, cognitive and motor effects is unclear (Harder, et al., 1997; Cone, et al., 1993). Dose and plasma concentration *vs.* response for possible therapeutic applications are ill-defined, except for some information obtained for oral dosing with dronabinol (synthetic THC) for its limited indications (Compendium of Pharmaceuticals and specialties, 2003). Interpretations of THC pharmacokinetics is also complicated by the emergence of active metabolites, particularly 11-hydroxy THC (Wall, et al., 1981; Cone, et al., 1988), which attains higher concentrations after oral than inhalation doses. Pharmacodynamic modelling (Barnett, et al., 1982) supports a 10 ng/mL cutoff as evidence of functional impairment (McBay, 1985) which is in agreement with the estimate of 25 – 29 ng/mL for the steady state plasma concentration at 50% of the maximum “high” effect, or  $C_{ss}(50)$ . The model was also used to simulate multiple dosing with a 1% cigarette containing 9 mg THC (Harder, et al., 1997). The duration of maximal “high” for this dose was estimated at about 45 minutes after dosing and declined to 50% of this peak effect at about 100 minutes following smoking. A dosing interval of 1h with this dose would give a “continuous high” and the recovery after the last dose would be 150 minutes. The peak plasma concentration during this dosage is estimated at about 70 ng/mL and the  $C_{ss}(50)$  at about 30 ng/mL THC.

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. However, it is likely that the psychoactivity that elicits this response from the central nervous system is receptor derived and the concentrations are useful for suggesting doses from smoking.

## **3.0 Dosing**

### **3.1 Smoking**

The actual dose of THC absorbed when smoked is not easily quantified (see section 2.2.1). According to the World Health Organization (World Health Organization, 1997), 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 actual amount of THC delivered in the smoke has been estimated at 20 to 70%, the remainder being lost through combustion or side stream smoke. The bioavailability of THC (the fraction of THC in the cigarette which reaches the bloodstream) from marijuana cigarettes in human subjects has been reported from 5 to 24%. The amount of other cannabinoids present, mainly CBN and CBD, is usually much lower, but the amount delivered and absorbed parallels that of THC.

Table 2 shows some relationships between percentage of THC in cannabis plant material and the amount in average joints. Bioavailability of cannabinoid depends greatly on smoking technique (likely maximum approximately 50%).

<b>Table 2: Relationship of THC percent in plant material to available dose in a joint</b>	
<b>%THC (mg per 100 mg cannabis)</b>	<b>mg THC per 750 mg* (“ average joint”)</b>
1	7.5
2.5	18.75
5	37.5
10	75
15	112.5
20	150
30	225

\* WHO average weight

Assuming the desired peak plasma concentration of smoked THC is in the 50-100 ng/mL range, (see Section 2.3) it has been shown (Huestis, et al., 1992) that this can be readily achieved with smoke from a single 3.55 % marihuana cigarette with about 900 mg plant material (approximately 32 mg THC).

A 750 mg joint of 5% strength (i.e., 37.5 mg THC) would yield slightly higher plasma levels. If the current average “street” marihuana 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 concentrations above 300 ng/mL. Clearly even more potent strains of cannabis have been reported. **Patients initiating smoked marihuana therapy should be cautioned to begin slowly and to stop smoking if tachycardia occurs.**

### 3.2 Oral

The pharmacokinetic information described in section 2.2 reports the erratic and slow absorption from the oral route and doses are estimated from the information for Marinol<sup>®</sup>.

### 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<sup>®</sup>. It is indicated for treatment of chemotherapy-induced emesis and for appetite stimulation in AIDS- related anorexia associated with weight loss (Compendium of Pharmaceuticals and Specialties, 2003; Marinol US monograph).

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

#### **4.1 Nausea and vomiting**

The IOM (National Academy of Sciences, 1999, p 4.17) and other committees (Health Department, NSW, Australia, 2000, p 41) consider that the place (if any) for smoked marijuana would be as an adjunct to other antiemetics, when they are not fully successful in treatment. However, there are no trials available for guidance. The BMA report (British Medical Association, 1997, p 27) indicates the research needed to evaluate marijuana in chemotherapy-induced emesis. This includes establishing dose ranges for cannabinoids and clinical trials to differentiate optimum cannabinoid treatment for specific anticancer agents and patient groups.

The IOM report suggests that, since there are now more effective antiemetic agents available than were available in the 1980s (especially the 5-HT<sub>3</sub> receptor antagonists), patients are less in need of THC.

#### **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 reports that marijuana is beneficial for patients with AIDS wasting syndrome are anecdotal, although it appears to be very popular with AIDS patients (Grinspoon et al., 1993). Studies with healthy subjects confirm an appetite stimulating effect of smoked marijuana together with increases of food consumption and body weight (Mattes, et al., 1994; Foltin, et al., 1988). In a controlled, residential laboratory study in which food consumption was carefully monitored and cannabis cigarettes were smoked with a standardized procedure, subjects consumed significantly more calories daily compared to placebo (Foltin, et al., 1988). There are, however no clinical trials of the smoked drug for this indication (National Academy of Sciences, 1999, p 4.19).

Oral synthetic THC, dronabinol, administered as capsules (Marinol<sup>®</sup>) has been approved for this indication. The Marinol product monograph summarizes a randomized double-blind, placebo controlled-trial in 139 patients (Beal, et al., 1995) with the 72 patients in the treatment group initially receiving 2.5 mg dronabinol twice a day, but then having the dose reduced to 2.5 mg at bedtime due to side effects (feeling high, dizziness, confusion and somnolence). Over the six week treatment period dronabinol significantly increased appetite, with a trend towards improved body-weight, and mood, and a decrease in nausea. After the six weeks, patients were allowed to continue receiving dronabinol, during which the appetite improvement continued.

A major concern with marijuana smoking in HIV-infected patients is that they might be more vulnerable than other marijuana users to immunosuppressive effects of marijuana or to the exposure of infectious organisms associated with marijuana plant material (National Academy of Sciences, 1999, p 4.19). There are also drug interaction concerns that are reviewed later.

#### **4.2.2 To stimulate appetite and produce weight gain in cancer patients**

Smoked marijuana has not been studied in patients with cancer cachexia. Oral THC (dronabinol) has been shown to improve appetite and food intake from observations during the investigations of the anti-nausea effect (Ekert, et al., 1979; Sallan, et al., 1980). Improved appetite and increased food intake was reported in patients with unresectable or advanced cancer treated with open-label dronabinol 2.5 mg 2 to 3 times daily for 4 to 6 weeks, but weight gain was achieved in only a few patients (Plasse, et al., 1991; Wadleigh, et al., 1990, p 331; Nelson, et al., 1994). Modest weight gain was obtained with a larger dose regimen of dronabinol (5 mg, 3 times daily), but the CNS side effects including dizziness and somnolence were limiting (Regelson, et al., 1976). Cancer cachexia is not an approved indication for dronabinol either in Canada or the U.S.

The immunomodulating effects of some cannabinoids could be contraindicated in some cancer patients (both the chemotherapy and the cancer can be immunosuppressive) (National Academy of Sciences, 1999, p 4.21).

#### **4.2.3 Anorexia nervosa**

A randomized trial of oral THC (Gross, et al., 1983) was unsuccessful for weight gain and three of the eleven patients administered THC reported severe dysphoric reactions. Both the British Medical Association (British Medical Association, 1997, p 46) and IOM (National Academy of Sciences, 1999, p 4.21) conclude that marijuana is unlikely to be effective in this group of patients.

### **4.3 Multiple sclerosis, spinal cord injury or disease**

The common symptom of these diseases is muscle spasticity. There are many anecdotal reports that marijuana can ameliorate spasticity associated with multiple sclerosis or spinal cord injury when other drugs fail or produce unacceptable side effects (American Medical Association, 1997, p 10; British Medical Association, 1997, p 30; National Academy of Sciences, 1999, p 4.23).

#### **4.3.1 Multiple sclerosis (MS)**

Published reports spanning one hundred years suggest that people with spasticity may experience relief with cannabis (Consroe, et al., 1986). As many as 4% of MS patients in the UK already smoke cannabis to relieve symptoms (Iverson, 2000, p 157) and in a mail survey of 233 MS patients in the UK and US, 112 (48%) reported (Consroe, 1997) that cannabis was used to ameliorate symptoms.

### **4.3.2 Spinal cord injury**

Patients surviving spinal cord injuries are usually young (60% are less than 35 years old (National Academy of Sciences, 1999, p 4.28)), and require long-term or even life-long care. While there are no clinical trials of smoked marijuana for treatment of muscle spasms, spinal patients reported to the IOM workshops that muscle spasms, nausea and sleeplessness were alleviated by smoking marijuana.

### **4.4 Epilepsy**

While some work in animals suggests that cannabinoids could have a role in treatment of some types of epileptic seizures (Consroe, et al., 1992), (in particular CBD appeared to have anticonvulsant without psychoactive properties (Hollister, 1986)), there are only anecdotal and individual case reports that marijuana controls seizures in epileptics.

The potential antiepileptic activity of cannabidiol (CBD) in epileptic patients who were poorly controlled with conventional anticonvulsants, has been investigated but is not promising (Ames, et al., 1986, p 14; Tremblay, et al., 1997, p 51; Cunha, et al., 1980).

### **4.5 Pain**

#### **4.5.1 Cancer pain**

There are no controlled clinical trials of smoked marijuana in treatment of pain. There are two double-blind, controlled studies of oral THC (dronabinol, Marinol<sup>®</sup>) in cancer pain. The first (Noyes Jr., et al., 1975) was a dose ranging study of 5, 10, 15 and 20 mg THC, given in successive days, to ten cancer patients. Significant pain relief was found at the 15 and 20 mg dose levels, but at these higher doses patients were heavily sedated with mental clouding common. A second, placebo-controlled, study (Noyes, et al., 1975) compared oral 10 and 20 mg THC with 60 and 120 mg codeine in 36 patients with cancer pain. The 10 and 20 mg THC were equivalent in analgesic potency with 60 and 120 mg codeine respectively. The 10 mg THC dose was well tolerated and, despite its sedative effect, may have analgesic potential, but the 20 mg THC dose induced side effects including somnolence, dizziness, ataxia, and blurred vision. Alarming extreme anxiety was also observed at this dose. This side effect profile is supported by a report concerning a synthetic analogue of THC also tested in controlled trials (Staquet, et al., 1978). While it was equivalent in efficacy to codeine, it was not considered clinically useful because of the frequency of side effects.

#### **4.5.2 Other pain categories**

Intravenous THC (0.22 mg/kg and 0.44 mg/kg) administered to patients undergoing tooth extraction (Raft, et al., 1977) was compared to diazepam (0.157 mg/kg). High dose THC was least effective and diazepam most effective. Four patients preferred placebo to low dose THC. A study of oral CBD, 450 mg/day in divided doses, in 10 patients with chronic neuropathic pain (neuralgia, etc.) also found no significant pain relief (Lindstrom, et al., 1997, p 43). Receptor studies indicate that cannabinoids might be useful adjuncts to opioid analgesia (National

Academy of Sciences, 1999, p 4.8). Improvement in phantom limb pain has been documented (British Medical Association, 1997, p 43).

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 (Campbell, et al., 2001).

## **4.6 Other diseases and symptoms**

### **4.6.1 Movement disorders**

The endogenous cannabinoid system appears to be intricately involved in normal physiology, specifically in the control of movement, formation of memories and appetite control and may be involved in the pathology of several neurological diseases. The contribution of cannabinoids to Huntington's disease, Parkinson's disease and tremor has been reviewed (Glass, 2001).

#### **4.6.1.1 Dystonia**

No controlled study of smoked marijuana in dystonic patients has been published. However, there was a preliminary open trial (Consroe, et al., 1986, 30: 277-282) of an oral cannabinoid. CBD, administered in five dystonic patients (100 mg/day rising to 600 mg/day over 6 weeks), showed modest dose-related improvements in all five, but worsening of tremor and hypokinesia in 2 patients with co-existing Parkinson's disease. Results of a double-blind randomized, placebo-controlled study of a synthetic cannabinoid (nabilone) showed no significant reduction in dystonia (Fox, et al., 2002).

#### **4.6.1.2 Huntington's disease**

A double-blind, placebo-controlled trial (Consroe, et al., 1991) of oral CBD, 10 mg/kg/day in 15 patients with Huntington's disease found no beneficial effects of treatment .

#### **4.6.1.3 Parkinson's disease**

There are theoretical reasons from research on brain transmission pathways that support a role for cannabinoids in the treatment of Parkinsonism. However, the one published clinical trial of smoked marijuana (1 g cigarettes containing 2.9% THC) involving five cases of idiopathic Parkinson's disease (Frankel, et al., 1990, 53: 436) found no improvement in tremor after the patients smoked marijuana, whereas all subjects benefited from the administration of levodopa and apomorphine. A small randomized clinical trial of the synthetic cannabinoid, nabilone, in seven patients with Parkinson's disease found that the treatment reduced levodopa-induced dyskinesia (Sieradzan, et al., 2001).

#### **4.6.1.4 Tourette's syndrome**

Four case histories suggest that smoked marijuana use can reduce tics in Tourette's patients (National Academy of Sciences, 1999, p 4.32). In one report of 3 patients, it is hypothesized that beneficial effects of marijuana might have been due to anxiety-reducing properties of marijuana rather than to a specific anti-tic effect (Sandyk, et al., 1988, p 444-445). A randomized, double-blind, placebo controlled trial of single oral doses of THC (5, 7.5 or 10 mg) in 12 patients with Tourette's syndrome showed plasma concentration-related improvements in control of tics and obsessive-compulsive behaviour, with no serious side effects; although transient, mild side effects were noted in five patients (Muller-Vahl, et al., 2002). A related study showed that in contrast to healthy marijuana users, single doses of THC (5-10 mg) caused no cognitive impairment measured by objective tests in 12 patients with Tourette's syndrome (Muller-Vahl, et al., 2001).

#### **4.6.2 Glaucoma**

The high intraocular pressure (IOP) of glaucoma can be reduced by marijuana (oral or smoked) and there are a few reports from treatment of glaucoma patients (British Medical Association, 1997, p 55). One reviewer remarks (Green, 1998) that "smoking of marijuana plant material for the reduction of elevated IOP in glaucoma is ill-advised, given its toxicological profile." Research with cannabinoids, including the discovery of ocular cannabinoid receptors, could lead to improved agents for glaucoma treatment (Jarvinen, et al., 2002).

#### **4.6.3 Bronchial asthma**

While cannabinoids are bronchodilators, there have been very few studies of the bronchodilator effect in asthmatic patients. A double-blind, placebo-controlled study of smoked marijuana (2% THC), oral THC (15 mg) and isoprenaline (0.5%) in 14 asthmatic subjects showed reversal of experimental bronchospasm by bronchodilation which was almost equivalent (Tashkin, et al., 1976). However, tolerance to this effect developed after several weeks (Tashkin, et al., 1976).

Another single-blind investigation of smoked marijuana (0.9 and 1.9% THC) found that it caused significant and prolonged bronchodilation, but tachycardia occurred with the higher dose (Vachon, et al., 1976). It is clear that smoked marijuana is not suitable for chronic use in asthma because of bronchial irritation from various components of smoke (British Medical Association, 1997, p 60).

#### **4.6.4 Hypertension**

Cannabinoids cause postural hypotension, but tolerance to the cardiovascular effects develops rapidly and together with adverse effects would preclude their consideration as a treatment for long-term use in hypertension (British Medical Association, 1997, p 64).

#### **4.6.5 Psychiatric disorders**

Cannabis has been advocated as a treatment for anxiety, depression, sleep disorders and alcohol and opiate withdrawal symptoms (Iverson, 2000, p 172). Use is anecdotal and occurred before modern psychotherapeutic agents became available. One anecdote concerns relief of depression by smoking marijuana, with much faster mood alteration than from amitriptyline, a conventional antidepressant that usually takes some weeks to take effect (Grinspoon, et al., 1993). Trials for treatment of chemotherapy-induced nausea with cannabinoids have mentioned some antidepressant effect (Regelson, et al., 1976). However, these are offset by the potential for severe psychological side effects.

Anecdotal information and some animal studies suggest that cannabinoids may be useful in treatment of opiate withdrawal, but there are no clinical studies to support this indication (British Medical Association, 1997, p 64).

#### **4.6.6 Alzheimer's disease**

Two possible indications for cannabinoid treatment in Alzheimer's are to stimulate appetite (i.e., to combat food refusal) and improve behaviour. Although oral THC (dronabinol, Marinol<sup>®</sup>) has been investigated in 11 patients and showed efficacy (Volicer, et al., 1997), there are concerns about the known THC effects on memory of healthy adults in this condition in which memory is already diminishing. There are also obvious concerns about the fire hazards of smoking marijuana in cognitively impaired patients.

### **5.0 Contraindications**

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

### **6.0 Warnings**

The dose of marijuana is difficult to estimate and is affected by source of 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 feel disoriented or agitated. Experienced smokers are able to "titrate" their dose, but naïve smokers should take great care and be supervised.

Marijuana can produce physical and psychological dependence and has the potential for abuse. The drug has complex effects in the CNS. These can result in cognitive and memory impairment, mood changes, altered perception and decreased impulse control. Patients should be supervised when administration is initiated.

Any patient experiencing a psychotic reaction to marijuana 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. Such impairment can last for over 24 hours after using due to the long half-life of THC.

Pregnancy: Use of marihuana during pregnancy should be avoided as there is evidence of long term development problems in children exposed to marihuana *in utero*.

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

## **7.0 Precautions**

### **7.1 General**

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

- Marihuana should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia.
- Smoked marihuana is not recommended in patients with respiratory insufficiency such as asthma or chronic obstructive pulmonary disease.
- Marihuana should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse marihuana, which itself, is a frequently abused substance.
- Patients with mania, depression, or schizophrenia should be under careful psychiatric monitoring if marihuana is taken, because it may exacerbate these illnesses.
- Marihuana should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.
- Patients should be advised of the negative effects on memory and to report any mental or behavioural changes that occur after using marihuana.

### **7.2 Dependence and withdrawal**

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

### **7.3 Special populations**

Marihuana should be used with caution in pregnant, pediatric and elderly patients, because there is insufficient knowledge about its use in these patient populations and the

potential for harm is likely to outweigh benefits (see Warnings, Pregnancy and Lactation).

#### **7.4 Drug interactions**

THC and CBD are metabolized by the cytochrome P450 system and *in vitro* human microsomal studies have suggested a potential for interaction with other drugs. CBD has been shown to inhibit formation of THC metabolites catalyzed by CYP 3A with less effect on CYP 2C9. For this reason there is concern that in patients undergoing multiple drug therapy, such as treatment of AIDS or cancer, clinically significant drug interactions might occur. However, both with dronabinol and smoked marijuana clinically significant interactions have not been detected. Protein binding is another possible source of interaction and patients exposed to marijuana should be monitored for a change in dosing requirements if they are taking other drugs that are highly protein-bound.

#### **7.5 Drug screening tests**

Because of the long half-life of elimination of cannabinoids and their metabolites, drug screening tests can be positive long after using marijuana (weeks with some tests).

### **8.0 Adverse Effects**

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

#### **8.1 Carcinogenesis, mutagenesis and respiratory tract**

The only epidemiological study in relatively young health maintenance organization (HMO) clients found an increased number of men with prostate cancer in smokers of cannabis and other non-tobacco materials. In this study, limited by the demographics of the HMO clientele and the low marijuana exposures, there were no other associations found between marijuana use and other cancers (Sidney, et al., 1997). A case control study (Zhang, et al., 1999) suggested that marijuana use may increase the risk of head and neck cancer with a strong dose-response pattern. The risk was increased 36-fold in those using both marijuana and tobacco compared to non-smoking controls. There has also been a rise in the number of cancers of the respiratory and digestive systems that are rare in young patients and are attributed to marijuana smoking (Hyman, 1999; Hall, et al., 1998). In addition there are many cellular and molecular studies that provide strong evidence that smoked marijuana is carcinogenic (National Academy of Sciences, 1999, p 3.41).

Epidemiological studies have found mild pulmonary function changes in heavy cannabis smokers, including reduction of forced expiratory volume in 1 second (FEV<sub>1</sub>), increase in airway resistance and decrease in airway conductance (Bloom, et al., 1987; Roth et al., 1998; Tashkin, et al., 1987). Heavy chronic smokers presented with symptoms of bronchitis, including wheezing, production of phlegm and chronic cough and it may be a risk factor for chronic obstructive pulmonary disease in later life (Hall, et al., 1998; Taylor, et al., 2002). All changes were most evident in heavy chronic users, defined as

those who smoked more than 3 joints per day for 25 years (Sidney et al., 1997; Tashkin, 1999). The effects on the respiratory tract defence system may increase the risk of infection in chronic users (Denning, 1991). Thus although additional epidemiological studies are required to determine the potential causal relationship between marijuana use and the development of respiratory infection and/or cancer, evidence is mounting that habitual smoking of marijuana has a number of adverse effects on the respiratory and immune systems (see below) that may be clinically relevant (Tashkin, et al., 2002).

## **8.2 Immune system**

The effects of marijuana smoking on the immune system are inconclusive. Among patients suffering from AIDS, the increased mortality and reports of opportunistic bacterial and fungal infections associated with marijuana use cause concern. Reviews suggest (Cabral, 2001; Klein, 2001) that such patients may be exposed to more pathogens or that the immune system is suppressed by marijuana (National Academy of Sciences, 1999, p 3.39).

## **8.3 Reproductive and endocrine systems**

Results of human epidemiological studies have been conflicting; some report reduced birth weight (Zuckerman, et al., 1989) and others no effect on birth weight (Shiono, et al., 1995) among women who smoked cannabis during pregnancy. There appears to be some long-term effects on development of children born to mothers who used marijuana during pregnancy. Two longitudinal investigations over 20 years (Fried, 2002), confirmed by a third (Richardson, et al., 2002), suggest that such *in utero* exposure impacts negatively on attentional behaviour and visual analysis/hypothesis testing but not on standardized derived IQ scores. In later years these behavioural effects have a negative influence on aspects of executive function. Also, frequent maternal cannabis use may be a weak risk factor for sudden infant death syndrome (SIDS) (Scragg, et al., 2001).

There is little information concerning transfer of cannabinoids and their metabolites in human milk (Chao, et al., 1976; Perez-Reyes, et al., 1982). However, in habitual maternal users of marijuana the above influences in development and behaviour would also be relevant. In a case-control study (Astley, et al., 1990), 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.

## **8.4 Cardiovascular effects**

The most consistent acute physiological effect of smoking marijuana is dose-related tachycardia (Trouve, et al., 1999). While cardiovascular changes have not usually been a problem for healthy young users, the tachycardia induced by cannabis smoking may be problematic to those already suffering from cardiac disorders or angina (National Academy of Sciences 1999 p 3.44). It was found that inhalation of cannabis smoke reduces the amount of exercise required to cause an attack by 50% (Aronow, et al., 1974). Recently, marijuana has been associated with an increased relative risk of nonfatal myocardial infarction in the first hour following smoking (Mittleman, et al.,

2001). This may be due to increasing myocardial oxygen demand from the increase in heart rate following cannabis use. However, other drug use could confound reports (Hollister, 1998).

Cannabis is known to cause postural hypotension immediately after smoking (Merritt, et al., 1982). It also causes peripheral vasodilatation, which can impact on body temperature perception and is involved in characteristic conjunctival reddening. The mechanisms for those effects on the autonomic nervous system are not understood (National Academy of Sciences, 1999p 3.44).

Chronic marijuana smoking appears to induce tolerance to the cardiac accelerating effect. In fact, after about 8 days of constant dosing with equivalent of 10 mg of THC per day (equivalent to 100 mg of marijuana containing 10% THC), bradycardia with hypotension (decrease in supine blood pressure) was observed (Chesher, et al., 1999).

THC and smoked marijuana poses health risks to people with cardiovascular disease because of the resulting increased cardiac work, increased catecholamine levels, carboxyhemoglobin and postural hypotension (Trouve, et al., 1999; Jones, 2002; Sidney, 2002).

AIDS patients may be at risk of cardiovascular effects from interactions of their antiviral drugs, such as ritonavir, which has been shown to cause plasma lipid abnormalities that increase risk of cardiovascular events (Purnell, et al., 2000). As this patient population may use cannabis for weight gain or other amelioration of symptoms, the additional cardiovascular effects from the marijuana should be considered in risk assessment.

## **8.5 Central nervous system**

According to the Marinol<sup>®</sup> (oral THC) product monograph, the most commonly encountered CNS events in controlled clinical trials were drowsiness, dizziness and transient impairment of sensory and perceptual functions (Compendium of Pharmaceuticals and Specialties, 2003). Psychotropic effects were observed in most patients; these included the “high” (easy laughing, elation, heightened awareness) in 24% of the THC group. Five percent of patients in the THC group and none in the placebo group experienced weakness or sluggishness, hallucinations, memory lapse and ataxia. Other events reported were dry mouth, paresthesias, visual distortions (all at 3%), paranoia, depersonalization (each 2%) and disorientation with confusion (1%).

### **8.5.1 Cognition**

Marijuana impairs cognition involving short-term memory, attention and concentration. 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 (% THC), the smoking procedure or whether the digit span task assesses forward or backward recall (Heishman, et al., 1989).

Methodological issues have contributed to difficulties in assessing the effects of

chronic use (Pope Jr, et al., 1995). However, overall, studies suggest that chronic users of marijuana suffer varying degrees of cognitive impairment that can be long lasting (Hollister, 1998). Cannabis intoxication significantly impairs the ability to learn and recall word lists or short stories. Recent studies comparing 51 long-term marijuana smokers (mean age 24 years) with nonsmoking and short-term user controls have confirmed that deficits in attention and memory occur with heavy cannabis use, and that these continue beyond the period of intoxication and are cumulative with longer periods of use (Solowij, et al., 2002).

### **8.5.2 Psychomotor performance**

Cannabis exposure impairs psychomotor performance and patients must be warned not to drive after smoking marijuana. The period of time to abstain from operating complex machinery depends on the dose, the disease being treated and the patient's age and gender. Individuals are affected differently by prolonged exposure to marijuana and there is some evidence of greater effects on adolescents. Discrimination of marijuana's effects from the normal effects of aging on cognition and performance has not been fully researched (Solowij, et al., 1999). Performance impairment appears to be less among people who are heavy users of cannabis compared to occasional users (National Academy of Sciences, 1999, p 3.8). It has been suggested that, unlike alcohol, cannabis users are aware of their level of intoxication and compensate to become hyper-cautious, resulting in decrease of speed, decreased frequency of overtaking as well as an increase in following distance (Gieringer, 1988). Others disagree with this assertion (Moskowitz, 1985).

### **8.5.3 Behavioural effects**

#### **8.5.3.1 Psychiatric disorders**

It is noted in the Marinol<sup>®</sup> (dronabinol, oral THC) product monograph (Compendium of Pharmaceutical and Specialties, 2003) that this drug should be used with caution and careful psychiatric monitoring in patients with mania, depression or schizophrenia because Marinol<sup>®</sup> may exacerbate these illnesses. This reflects the IOM report (National Academy of Sciences, 1999, p 3.23, 3.29) and also the knowledge that psychiatric disorders are associated with substance dependence and are risk factors for drug abuse.

Acute toxic reactions such as nausea, anxiety, paranoia and disorientation often occur in naïve marijuana smokers but are uncommon in regular users (Noyes Jr, et al., 1975). The triggering of psychosis by marijuana has not been definitively established, but it appears that cannabis is frequently used by psychotic patients (Hollister, 1998). Heavy cannabis smoking, and even lighter use in susceptible individuals, can produce an acute psychosis including anxiety, agitation, amnesia, delusions, hallucinations and hypomanic symptoms (Australian Commonwealth Government, Department of Health and Ageing, 1994).

### **8.5.3.2 Schizophrenia**

Self-reported use of cannabis in childhood has been associated with an increased risk of developing schizophrenia and this risk was related to frequency of marijuana exposure (Zammit, et al, 2002). A cohort study of over 1000 children, followed to age 26 from birth, showed a three-fold increased risk of psychotic disorders in cannabis users and suggested that cannabis exposure among psychologically vulnerable adolescents should be strongly discouraged (Arseneault, 2002, p 1212-1213). Heavy marijuana use can aggravate symptoms and cause more relapses (Alleback, 1999; National Academy of Sciences, 1999, p 3.29). Follow-up studies confirm the increased risk of poor prognosis in psychosis for those using marijuana (Caspari, 1999; van Os, et al., 2002). 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 (Johns, 2001).

### **8.5.3.3 Amotivational syndrome**

This syndrome is used to describe young people who show little interest in school, work or other goal-oriented activity as well as withdrawing from social activities. While it is an ill-defined condition, this is a common feature of chronic intoxication with many different psychoactive drugs and when the chronic intoxication is treated or “cured” the behaviour improves. There is no convincing evidence to show a casual relationship between marijuana smoking and such behavioural characteristics (National Academy of Sciences, 1999, p 3.31).

### **8.5.3.4 Dependence and tolerance**

Tolerance to most of the effects of marijuana can develop after a few doses and it also disappears rapidly (National Academy of Sciences, 1999, p 3.8). In normal subjects tolerance develops to mood, intraocular pressure, EEG changes, psychomotor performance, antiemetic effects (Jones, et al., 1976) as well as to cardiovascular effects (Compton, et al., 1990). The dynamics of tolerance differs for different effects (Pertwee, 1991). Tolerance to some of the cannabis effects develops both when THC is administered orally (30 mg four times a day) and when a roughly equivalent dose was given by smoking (Haney, et al., 1999) (3.1% cigarette, 5 x 10 second puffs). Both groups became tolerant to the “high”, but there was no diminution of the appetite stimulating effect from either route of administration.

There is evidence that cannabis dependence occurs with chronic heavy recreational use. Some individuals report problems in controlling such use despite resulting personal difficulties (Australian Commonwealth Government, Department of Health and Ageing, 1994; Stephens, et al., 1993). Dependence is unlikely to be problematic when cannabis is used therapeutically although

withdrawal effects may be uncomfortable (British Medical Association, 1997, p 67). These include restlessness, anxiety, mild agitation, irritability, tremor, insomnia and EEG/ sleep disturbance, nausea, diarrhea and cramping. Withdrawal has been studied in subjects, including adolescents who smoked marihuana recreationally (Crowley, et al., 1998). These effects are considered mild compared to the physical “syndromes” experienced with alcohol or opiate withdrawal (Jones, et al., 1976) and the pattern of withdrawal is less clear than for these drugs (Smith, 2002).

### **9.0 Overdose/Toxicity**

The LD<sub>50</sub> is estimated to be 20,000 to 40,000 times the amount in one marihuana cigarette (approximately 1500 lb) smoked in a period of 15 minutes (Annas, 1997). Marihuana is not a completely benign agent and it has a variety of physiological effects, but aside from the hazards consequent to smoking, the adverse effects are within the range tolerated for other medications (National Academy of Sciences, 1999, p3.49). Cannabis often produces unwanted effects, typically dizziness, sedation, intoxication, clumsiness, dry mouth, lowered blood pressure or increased heart rate (Robson, 2001). The rare acute complications (such as panic attacks, psychosis, convulsions, etc.) that present to the Emergency Department can be managed with conservative measures (Seldon, et al., 1990). As is stated for overdose with Marinol<sup>®</sup> (Compendium of Pharmaceuticals and Specialties, 2003), signs and symptoms with smoked marihuana are an extension of the psychotomimetic and physiologic effects of THC. If disturbing psychiatric symptoms occur at the prescribed dosage, the patient should be closely observed in a quiet environment and supportive measures, including reassurance, should be used.

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